Dominance reversals, antagonistic pleiotropy, and the maintenance of genetic variation

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Abstract

The last decade has seen increasing theoretical and empirical support for beneficial reversals of dominance enabling selection to maintain genetic variation for fitness through various forms of antagonistic pleiotropy. Such dominance reversals are characterized by the beneficial allele for a given context (e.g., spaces, times, tissues or sexes) being dominant in that context. This context-dependence at least partially mitigates the fitness consequence of heterozygotes carrying one of the ‘wrong’ alleles for their context, and can result in balancing selection that maintains both alleles. Despite being dismissed by many early on, dominance reversals are an inevitable outcome under reasonable assumptions, and mounting empirical evidence largely supports this theory. Here we review the theory and empirical evidence for beneficial reversals of dominance. Along the way, we identify some areas in need of further development, point out some complications with detecting antagonistic pleiotropy, and highlight two empirical methods that leverage signatures of dominance reversal toward identifying patterns of antagonistic pleiotropy in quantitative genetic and transcriptomic data. There is ample scope for the development of new empirical methods that focus on signatures of dominance reversal, and there is likely also an abundance of data that are ripe for reanalysis. A greater focus on this topic would expand our understanding of the maintenance of genetic variance and local adaptation.
Introduction

Explaining the maintenance of genetic variance in fitness has been a mainstay pursuit in evolutionary biology since the modern synthesis. Mutation rates are typically too low for mutation-selection balance to account for all of the observed genetic variance in fitness and its components. Selection must therefore maintain, or at least slow the loss of, genetic variation for fitness throughout the genome. Antagonistic pleiotropy can generate balancing selection and maintain genetic variation, but only under quite restrictive conditions given the simplest set of assumptions (see below). However, the conditions for balanced genetic polymorphisms under antagonistic selection are substantially broadened when the allele that benefits fitness in a given context is also dominant in that context. Consider a bi-allelic locus in which one allele imposes a relative benefit to survival but detriment to reproduction (and vice versa for the other allele), the polymorphism would tend to fix according to whichever fitness component (survival or reproduction) is under stronger selection, unless the beneficial survival-effect of the first allele were dominant and its detrimental effect on reproduction were recessive (and vice versa for the opposite allele). Such beneficial reversals of dominance were met with skepticism early on, but have since seen considerable theoretical and empirical evidence (reviewed herein).

At first it may seem too good to be true that a novel mutation could be dominant when/where it benefits fitness yet recessive when/where it is deleterious, but basic theoretical principles and empirical evidence are shifting our understanding of this phenomenon from fortuitous and rare to inevitable and favored by selection. Since the empirical evidence is distributed broadly over a variety of sub-disciplines with little or no interdisciplinary awareness, the summed wealth of evidence supporting dominance reversal is missing from the literature. Below we review this unifying theoretical and empirical evidence for dominance reversal, and highlight novel empirical methods for its detection, which may provide more promising avenues toward identifying antagonistic polymorphisms in the genome than methods based on additivity. Given the elusiveness of antagonistic polymorphisms in the genome, as well as the magnitude of genetic variance that antagonistic pleiotropy can generate and the growing evidence
for the dominance reversals, such genetic tradeoffs likely play an underappreciated role in maintaining genetic variance and enabling local adaptation.

_A Primer on Antagonistic Pleiotropy_

The alternative contexts in which an allele could pleiotropically affect fitness could be alternative traits of a single individual\textsuperscript{21–23} (e.g., survival versus reproduction), or could be alternative niches, time points or environments\textsuperscript{15,18,28,32,33}, including the male versus female environment\textsuperscript{20}. A novel mutation that is selected positively in one context will tend to be selected negatively in another context (i.e., will tend to be antagonistic) if it pleiotropically affects fitness in both contexts\textsuperscript{34–36}. This assertion is a direct extension of Fisher’s\textsuperscript{37,38} geometric model\textsuperscript{39,40}. That is, just as most spontaneous mutations will have a deleterious effect on fitness, a rare mutation that happens to benefit fitness in one context via its effect on some trait’s expression is most likely to harm fitness in another context or trait that is pleiotropically affected. Studies of microorganisms show that adaptations to a given context or environment typically come at the cost of reduced fitness in other contexts\textsuperscript{41} (but see\textsuperscript{42}), a pattern that is expected to be more widespread with increasing organismal complexity due to there being more contexts (i.e., tissues, traits, sexes, etc.) over which such tradeoffs could ensue\textsuperscript{43–45}. Accordingly, there is abundant evidence in multicellular eukaryotes that is consistent with antagonistic genetic variation underlying some proportion of variance in a trait or fitness, for example via tradeoffs between fitness components or life history traits\textsuperscript{46,47}, tissue types\textsuperscript{48,49}, reproductive strategies\textsuperscript{50}, environments, spaces or times\textsuperscript{51–54}. In particular, sexually antagonistic pleiotropy, where alternative alleles are favored oppositely by the sexes\textsuperscript{20,26,55,56}, has accrued a wealth of empirical\textsuperscript{57–73} and theoretical\textsuperscript{26,35,36,74–103} support in recent decades.

Evidence of antagonistic genetic variation does not imply balanced polymorphisms that would be maintained by selection indefinitely – many of the underlying polymorphisms likely will not meet the conditions for balancing selection, but the relative proportion of them that are balanced may largely
depend on the relative likelihood of dominance reversals (addressed herein). Regardless of whether or not the underlying antagonistic polymorphisms are balanced, antagonistic selection will still maintain greater levels of additive genetic variance in fitness than both directional selection and classical forms of balancing selection (i.e. overdominance, heterozygote advantage). This is because the less fit allele, being beneficial in some context, is more slowly removed from the population than an unconditionally deleterious allele. Likewise, partial selective sweeps occur more slowly (have slower transit times) under antagonistic balancing selection than under overdominance/heterozygote advantage. This slower, non-directional sweep characteristic of antagonistic genetic variation causes weaker genomic signatures of selective sweeps when local adaptation occurs in variable environments (as is likely common in nature), as well as weaker genomic signature of balancing selection even when such conditions are met. That is, antagonistic pleiotropy can result in both local adaptation and balancing selection, but conventional methods for detecting those processes in the genome are biased toward identifying signatures attributable to directional selection and overdominance, respectively. Hence, our ability to detect the action of antagonistic genetic variation in the genome may be dwarfed by its relative presence, as seems to be the case for sexually antagonistic genetic variation considering the abundant quantitative genetic evidence of its presence. Thus, as discussed below, directly investigating genomic or quantitative genetic signatures of dominance reversal may actually be a more promising, or at least complimentary, method for detecting balancing selection and local adaptation stemming from antagonistic pleiotropy.

Regarding the role of antagonistic genetic variation in local adaptation, we note that it is classically and intuitively interpreted as a constraint to, rather than enabler of, local adaptation and sexual dimorphism (but see). However, this interpretation assumes additive genetic variance, an assumption that is called into question by recently accumulating empirical evidence for the non-additive process of dominance reversal (reviewed below), which can promote local adaptation directly by enabling proportionally more individuals in a population to be closer to their local context.
specific fitness optimum (see below)\textsuperscript{52,59}, or indirectly (as alluded to above) via its contribution to maintaining antagonistic genetic variation\textsuperscript{24,21,29} that can in turn enable local adaptation\textsuperscript{106}. Hence, the view that antagonistic pleiotropy would translate to adaptive constraints rather than adaptive potential may stem from a preoccupation with additive genetic variance, whereas much of the stored adaptive potential bestowed by antagonistic genetic variation may lie in the reversed dominance effects that in turn facilitate its maintenance.

The study by Ruzicka et al.\textsuperscript{60} carries several important implications. They identified hundreds of polymorphisms throughout the \textit{Drosophila melanogaster} genome that are associated with sexually antagonistic fitness variation, and then found those same polymorphisms to be shared with the sister species \textit{D. simulans} at a significantly greater rate than randomly selected site-frequency-matched polymorphisms\textsuperscript{60}. This implies that those sexually antagonistic polymorphisms arose prior to the speciation between \textit{D. melanogaster} and \textit{D. simulans} and have been maintained in both lineages by sexually antagonistic balancing selection\textsuperscript{60}. That pattern of shared sexually antagonistic polymorphisms was not seen in the more distantly related \textit{D. yakuba}\textsuperscript{60}. One important implication of their findings is as follows: for so many polymorphisms to be maintained by sexually antagonistic balancing selection – each having an individually miniscule effect on fitness – would seemingly require the assistance of dominance reversal since such weakly selected sites are highly susceptible to one or the other allele being fixed by drift or subtle imbalances in the strength of selection between the sexes (see next section). Another implication, pertaining to the previous paragraph and the use of the word “constraint,” is that while their evidence may represent an example of sexually antagonistic pleiotropy constraining genomic divergence, it need not actually constrain local adaptation (in this case sexual dimorphism), since the likely role of dominance reversal in maintaining such genetic variation would actually enable proportionally more individuals to be closer to their sex-specific fitness optima (e.g.,\textsuperscript{59}; explained below).
A Primer on Dominance Reversals

The capacity for a polymorphism with antagonistic fitness effects to constitute balancing selection and be maintained indefinitely drastically improves with beneficial reversals of dominance (Box 1), where the favored allele of a given context is at least partially dominant within that context\textsuperscript{20,21,29}. (It is worth emphasizing that unless otherwise stated the antagonistic effects that we refer to are antagonistic with respect to fitness; whether similar statements apply to antagonistic effects on some trait depends on the extent to which the trait determines fitness.) To maintain a single antagonistic polymorphism where the allelic effects are strictly additive for fitness (e.g., Fig. 1i) requires very strong antagonistic selection and/or symmetric selection coefficients across environments\textsuperscript{19–21,23,29} (Box 1). However, a beneficial reversal of dominance masks the deleterious fitness effects of each allele in its non-favored context, causing heterozygotes to have fitness above the average of both homozygotes (e.g., Fig. 1ii-iv). Such elevated fitness generates a net heterozygote-advantage scenario at the population-level\textsuperscript{20,21,29}, where the mean fitness of the population’s heterozygotes averaged across contexts is higher than that of either homozygote, even though the highest individual-fitness value may still be given by the ‘correct’ homozygote for a particular context in the case of niche- or sexual-antagonism (Fig. 1).
Box 1 | Dominance reversal theory

Maintenance of genetic variation
As seen in the figure to the right (reprinted with permission from Connallon and Chenoweth118), the parameter space of selection coefficients for which a simple additive antagonistic polymorphism is maintained (white regions within solid lines) is very narrow, especially for weak selection (right panel), but expands drastically to also include the grey areas within the dashed lines when alleles exhibit at least a partial beneficial reversal of dominance ($h_F = h_M = 1/4$). The example given is for sexually antagonistic selection20,118, but the same stabilizing effect of dominance reversal holds for antagonistic pleiotropy between fitness components21, randomly fluctuating selection29, and temporally fluctuating selection119, especially in conjunction with other stabilizing mechanisms120. Note that these results are regarding beneficial reversals of dominance for fitness, per se, and hence should not depend on whether that stems from dominance-reversed trait expression (e.g., Fig. 1ii), the curvature of the fitness landscape (e.g., Fig. 1iii), or both (e.g., Fig. 1iv).

Some uncertainties
As discussed in the main text, beneficial reversals of dominance could, in theory, owe to the concavity of the context-specific fitness functions in the vicinity of their overlap76,77,121 (Fig. 1D), to the adaptive invasion of a “dominance modifier”93 (Box 2), or both (e.g., Fig. 1iv). The fitness-landscape explanation is very intuitive and can be gleaned from comparing the results between Fig. 1i and Fig. 1iii. Yet, it is equally theoretically conceivable for two fitness functions to overlap in their convex vicinities (Fig. 1E), such as when the fitness optima of two Gaussian fitness functions are sufficiently far apart. Further, at very fine scales, such as the average fitness effect of individual loci122, curved fitness functions may be effectively linear (analogous to Taylor series approximation123), or as noted by Martin and Lenormand34 they could be less smooth (more rugged). Thus, while there are good theoretical and empirical reasons to think that fitness functions should be concave near their optima34,77,124–129, whether the overlap between two real fitness functions occurs in their concave, convex or linear portions (Fig. 1C-E) can only be resolved by empirical estimates of context-specific fitness functions.

Future directions
This brings the attention back to the role of “dominance modifiers” in generating beneficial reversals of dominance. However, while they are adaptive and should invade given high enough frequency of heterozygotes at the focal antagonistic polymorphism93, what exactly is meant by the term “dominance modifier” has never been clear. In principle this could be any genetic or epigenetic process that affects the dominance properties of an otherwise additive polymorphism. In reality, however, there are currently no empirical examples, to our knowledge, of a dominance modifier that generates beneficial reversals of dominance. A theoretical exploration of one biophysically explicit possibility is presented in Box 2.
Fig 1: Theoretical framework for dominance reversal between niches or sexes. An array of scenarios by which beneficial or detrimental dominance reversals for fitness could arise: we first map genotype to phenotype (A,B), then phenotype to fitness (C,D,E), and then combined those to attain the genotype-fitness mapping (i-vi). Circles versus triangles represent alternative niches or sexes. Grey to black shading represents arbitrary parameter settings (|DD| = absolute value dominance deviation from additivity; G = the exponential scaling of the fitness landscape). A) Additive genotype-phenotype relationship in both contexts. B) Heterozygotes exhibit a context-dependent dominance reversal for expression (e.g.,\textsuperscript{59}). C) A simple additive fitness landscape. D) Context-specific fitness functions overlap in their concave vicinity, conducive to a beneficial reversal of dominance\textsuperscript{76,77,121}. E) Context-specific fitness functions overlap in their convex vicinity, conducive to a detrimental reversal of dominance. For example, additivity for both genotype-phenotype (A) and phenotype-fitness (C) will yield an additive genotype-fitness relationship (i), whereas dominance reversal for expression (B) and/or a concave-overlapping fitness landscape (D)
could yield a beneficial reversal of dominance for fitness (ii-iv). In principle, a dominance-reversed genotype-expression relationship (B) combined with a convex-overlapping fitness landscape (E) could yield an additive, detrimental or beneficial reversal of dominance for fitness depending on the underlying parameter values (vi). All possible scenarios are not shown, namely, dominance reversal between individual fitness components\textsuperscript{21}, which could yield overdominance for fitness. See Data Archiving for R code.

Dominance reversal between antagonistic alleles may simply owe to the shape of the fitness landscape (Fig. 1iii). That is, for a trait under antagonistic pleiotropy, dominance reversals will ensue at the underlying polymorphic loci if the context-specific fitness functions overlap in their concave vicinities\textsuperscript{76,77,121} (Fig. 1, Box 1). There are good theoretical and empirical reasons to think that fitness functions are generally concave in the vicinity of their optima (Box 1). Given a concave fitness function, it is a well-established theoretical expectation with ample empirical support that beneficial alleles should be dominant and deleterious alleles should be recessive\textsuperscript{1,28–139}. Hence, while the concept of beneficial reversals of dominance emerging from overlapping concave fitness functions is an important theoretical development that emerged in recent decades\textsuperscript{76,77,121}, it has been hidden in plain sight for nearly a century. Still, the shape of the fitness landscape cannot be taken for granted (see Some uncertainties in Box 1), and there are empirical examples of dominance reversals occurring at the trait-level (e.g.,\textsuperscript{46,59}; reviewed below), keeping the discussion and research surrounding dominance modifiers of antagonistic polymorphisms alive and well.

A dominance modifier that causes a beneficial reversal of dominance at an otherwise additive antagonistic polymorphism (Box 2) is selectively favored, and will invade, if there is already a sufficiently high frequency of heterozygotes at the focal antagonistic site, as Spencer and Priest\textsuperscript{93} have shown for sexually antagonistic selection. This occurs because it at least partially mitigates the costs paid by heterozygotes of carrying one of the ‘wrong’ alleles for their context\textsuperscript{93}. This theory is an extension of Otto and Bourguet’s\textsuperscript{140} theory, and the concept ultimately dates back more than one hundred years, even prior to (but including) the classical Fisher-Wright debate\textsuperscript{93,141,142}. While selection in this case is acting at the individual-level, the population-level outcome is to protect the antagonistic polymorphism from being lost by drift or unequal selection between contexts, and therefore to maintain genetic variation for fitness\textsuperscript{93}. 
(Box 1). Similar criteria likely govern the adaptive invasion of dominance modifiers under other forms of antagonistic selection as well.
Box 2 | Dominance modifiers

Background
While dominance reversals can be born out of context-specific fitness functions overlapping in their concave vicinities76,77,121 (Fig 1iii), that favorable fitness landscape is not a theoretical inevitability and may not always be an appropriate assumption (Box 1). Further, some empirical evidence of dominance reversal occurs at the phenotypic level59 (as in Fig 1B,ii). Without ‘help’ from the fitness landscape, a dominance modifier may enable the scenario depicted in Fig 1i to become Fig 1ii. Such a dominance modifier is favored by antagonistic selection93 (see main text), begging the question of what molecular phenomena might characterize such a process. Porter et al.143 showed that Medelian dominance can arise when alternative transcription factor alleles compete for a downstream target substrate. An allele can be dominant via its superior binding affinity to the substrate, or via its superior allele-specific concentration143. It is worth exploring whether antagonistic selection can utilize these alternative avenues of dominance (i.e. binding affinity versus concentration) to enable alternative alleles to be dominant in alternative contexts, as well as whether that adaptive outcome exhibits any genomic or transcriptomic patterns.

A biophysically explicit model of a sex-specific dominance modifier
In the Supporting Information (S1) we show forward-time population genetic simulations of an arbitrary, but biophysically explicit, gene regulatory network to test whether selection can cause basic gene regulatory machinery to evolve dominance reversal and facilitate the maintenance of an antagonistic polymorphism. In our example, the alternative alleles of a focal sexually antagonistic transcription factor polymorphism (blue and orange alleles of Gene A, below) have opposite effects on the expression of Gene B, and Gene B’s expression is under additive sexually antagonistic selection (such as Fig 1C). As such, this focal polymorphism would be highly sensitive to fixing either allele (Box 1). We do not allow new mutation at that focal polymorphism as we are interested in its maintenance via the surrounding regulatory activity. Namely, Gene A’s cis-regulatory144 binding site (small grey rectangles) can mutate/evolve toward being a better binder of either the male- or female-limited regulatory stimuli (green and purple Ms and Fs), approximating sex-limited hormones or the alternatively spliced dsx or fru genes in insects145. There is no dominance coefficient (h); dominance between focal alleles is an emergent property of their fractional occupancy143 of Gene B’s binding site (small grey rectangles), a function of allele-specific concentrations and binding affinities (S1).

Results and future directions
Selection favors the adaptive haplotypes of Gene A that enable heterozygous males and females to adjust the expression of Gene B toward their sex-specific fitness optima (S1), resolving the genetic conflict59,93 (see Box 3). The resultant sex-specific dominance reversal for fitness maintains the focal polymorphism without any ‘help’ from the fitness landscape (as in Fig 1ii; S1). The sex-specific "dominance modifier" in this case may be thought of as the cis-regulatory binding site, but it relies on the surrounding regulatory network. As such, this slightly more realistic model could produce different insights to those of an analogous two-locus model in which the dominance modifier can simply adjust the sex-specific genotypic dominance parameterization (h)93. Lastly, our focal polymorphism exhibited a pattern of reversed allele-specific expression144 between the sexes (S1) – a detectable transcriptomic signature of dominance reversal.

This framework could be used to explore the invasion of dominance modifiers that enable context-specific reversals of dominance (as in 93), or of focal antagonistic alleles under some preexistent regulatory network. It could also be used for researching the quantitative genetic, genomic and transcriptomic patterns generated by antagonistic pleiotropy and dominance reversal. It can readily accommodate additional genes and/or branched regulatory networks (e.g., transcription co-factors and/or multiple downstream target sites). Lastly, such models could also help identify the likelihood of alternative regulatory networks (such as Friedlander et al.146 have done) and/or how gene duplications may compete with dominance reversals to resolve genetic conflicts (see Box 3).
Whether beneficial reversals of dominance owe to the fitness landscape\textsuperscript{76,77,121} (Fig 1iii, Box 1), dominance modifiers\textsuperscript{93} (Fig 1ii, Box 2), or both (e.g., Fig. 1iv), the consequence can be a net heterozygote-advantage (marginal overdominance) at the population-level in the case of niche- or sexual-antagonism, or even true overdominance (heterozygote-advantage) for fitness in the case of antagonistic pleiotropy between fitness components\textsuperscript{21} (e.g.,\textsuperscript{46,147}; reviewed below). At the individual-level, this represents at least a partial \textbf{resolution} to the \textbf{genetic conflict} (Box 3). This terminology is intuitive for the dominance modifier scenario\textsuperscript{93} (Box 2), in which adaptive evolution offers a solution to a problem (i.e., resolves a genetic conflict). It is perhaps less intuitive when dominance reversals stem from the fitness landscape, as the term “resolution” actually refers to the curved fitness landscape being the more adaptive scenario for heterozygotes relative to a hypothetical additive fitness landscape (i.e., Fig 1i versus Fig 1iii). Nevertheless, the long-term population-level consequence of antagonistic genetic conflicts being resolved by dominance reversal is to drastically expand the range of selection coefficients for which the underlying antagonistic polymorphisms are maintained in the face of random genetic drift and/or imbalances in the strength of selection between contexts\textsuperscript{20,21,29} (Box 1). This expansion of the parameter space is especially important when selection coefficients are small (Box 1), as is expected for the many loci presumed to underlie fitness and continuous traits\textsuperscript{122}.
Box 3 | Resolution of genetic conflict

Meaning of “genetic conflict”
Antagonistic selection will inevitably lead to reduced fitness in one or the other context, or both, as a result of selection in each context being blind to the fitness costs in the other. That is, each allele of an antagonistic polymorphism will have reduced mean fitness (averaged over contexts) relative to a scenario where we only consider the context in which that allele is favored. Such unresolved genetic conflict ultimately reduces population mean fitness, imposing a “segregation load” on the population.

An example
In the context of sexually antagonistic selection, male-benefit/female-detriment alleles will effectively reduce the population mean fitness if neither sex is able to achieve its optimum phenotype. This could reduce the population’s growth rate, which, in many species, is expected to be limited more so by its females’ offspring production than its males’ fertility. For example, in the seed beetle, *Callosobruchus maculatus*, genotypes enriched for male-benefit/female-detriment alleles suffered reduced offspring productivity, were less able to cope with temperature stress, and showed reduced tolerance to homozygosity. All of which can culminate in an extinction vortex. In that same species, populations with relatively greater sexual dimorphism in development rate—which indicates a partial resolution to the constraint imposed by shared developmental genetic architecture (or less sexually antagonistic selection)–exhibited relatively greater offspring productivity. By extension, other forms of antagonistic pleiotropy can impose a constraint to local adaptation if not for some mechanism that resolves this conflict.

Meaning of “resolution”
In principle, any process that enables some mitigation of individual-level genotype-by-environment fitness costs could be considered a resolution of the genetic conflict, such as plasticity in gene expression. Consider a gene (even an invariant gene) with sex-specific fitness optima for its expression level: the ensuing sexual conflict over the gene’s expression level is commonly thought to be resolved via the widespread observation of plastic gene expression between the sexes, known as sex-biased gene expression. Other mechanisms that can resolve genetic conflicts between the sexes include sex-linkage, parental imprinting, epigenetics, gene duplication, and dominance reversal—many of which work analogously in other forms of antagonistic selection.

Future directions
Whether different mechanisms compete for resolving genetic conflicts is of particular interest. For example, the capacity for gene duplications to resolve genetic conflicts hinges on whether the costs of the conflict are great enough, and therefore the degree to which those costs have already been mitigated by dominance reversal or other mechanisms. Whereas dominance reversals maintain genetic variation as a byproduct of resolving genetic conflicts, gene duplications result in the loss of genetic variation via the fixation of one allele at the ancestral locus and the other allele at the derived locus. Sometimes thought of as “fixed heterozygosity,” this can reduce the potential for dominance reversal to mitigate these costs. However, the maintenance of genetic variation and the evolution of genome architecture. Biophysically explicit models that combine the ability of genes or gene networks to duplicate with the ability of dominance modifiers to evolve may be particularly well-suited for understanding the ultimate effect of antagonistic selection on the genome.

Taking Ruzicka et al.’s study for example—one of the best genome-wide looks at (sexually) antagonistic pleiotropy for fitness—their evidence is consistent with hundreds of polymorphisms in *D. melanogaster* being maintained by antagonistic balancing selection (described above). This means that the selection coefficients for each polymorphism must be miniscule. Considering that dominance reversal is a particularly potent, nearly required, force for weakly selected antagonistic polymorphisms to be
maintained\textsuperscript{20} (Box 1), the long-term persistence of these polymorphisms detected by Ruzicka et al.\textsuperscript{60} may very well owe to sex-specific dominance reversals for fitness. Fittingly, a polygenic signal of sex-specific dominance reversal was demonstrated in the seed beetle \textit{Callosobruchus maculatus}\textsuperscript{72}. We note that small-effect antagonistic polymorphisms are counter to the classical understanding that antagonistic polymorphisms are likely to have large fitness effects, however, this understanding stems from skepticism over the plausibility of dominance reversals\textsuperscript{2,33,31}, which has left many evolutionary biologists to conclude that antagonistic polymorphisms could only possibly be maintained under strong selection coefficients\textsuperscript{19} (Box 1). The theoretical points made thus far and the empirical evidence reviewed below should counter this skepticism.

**Empirical Evidence**

Surprisingly, few studies have explicitly set out to test for beneficial reversals of dominance (with notable exceptions\textsuperscript{52}). Instead, it is a woefully understudied phenomenon where empirical support has mostly arisen unexpectedly, and is commonly overlooked or presented in a different light. The evidence lurks in studies that were not designed or written in light of dominance reversals and/or antagonistic pleiotropy\textsuperscript{46,159,176}. These are symptoms of it having been downplayed as a plausible evolutionary phenomenon and make it infeasible to provide a comprehensive review of the evidence. Instead, we have gathered empirical examples of dominance reversal that stem from somewhat disparate sub-disciplines (Table 1), highlighting them in detail in order to emphasize the different forms of evidence, different methodologies, and different areas of evolutionary biology that share this common interest. Below, we divide this discussion into \textit{Major-effect loci} and \textit{Polygenic evidence}. 
Table 1. Evidence for beneficial reversals of dominance

| Study                  | Species          | Evidence         | Context     | Data              | Method                                | Analysis                      |
|------------------------|------------------|------------------|-------------|-------------------|---------------------------------------|-------------------------------|
| Johnston et al. 2013   | Ovis aries       | Single locus     | Traits      | Fitness component | Pedigree / GWAS                      | Statistical modeling          |
| Le Poul et al. 2014    | Heliconius numata| Inversion / Polygenic | Traits      | Phenotypic        | Crossing scheme                       | Statistical modeling          |
| Posavi et al. 2014     | Eurytemora affinis| Polygenic        | Niches      | Fitness component | Crossing scheme                       | Statistical modeling          |
| Barson et al. 2015     | Salmo salar      | Single locus     | Sexes       | Fitness component | Capture-recapture / GWAS              | Statistical modeling          |
| Chen et al. 2015       | Drosophila melanogaster | Polygenic        | Niches      | Gene expression   | Transcriptomic                        | Allele-specific expression    |
| Grieshop and Arnqvist 2018 | Callosobruchus maculatus | Polygenic        | Sexes       | Fitness           | Crossing scheme                       | Dominance ordination          |
| Pearse et al. 2019     | Oncorhynchus mykiss | Inversion        | Sexes       | Fitness component | Capture-recapture                     | Statistical modeling          |
| Mérot et al. 2020      | Coelopa frigida  | Inversion        | Traits      | Fitness component | Experimental evolution                 | Statistical modeling / Numerical simulations |
| Jardine et al. 2021    | Drosophila melanogaster | Single locus     | Traits      | Fitness component | Genomics / phenotyping               | Statistical modeling          |

Major-effect loci

One of the turning points in the growing appreciation for the role of dominance reversals in evolution, Barson et al.\cite{59} interpreted their findings in the light of dominance reversal resolving genetic conflict (Box 3) and maintaining sexually antagonistic genetic variation for an important fitness component (Table 1). They identified a major-effect autosomal gene (VGLL3) in Atlantic salmon (Salmo salar) that explained 39% of phenotypic variation in age at sexual maturity – a life history trait that is presumably under sexually antagonistic selection\cite{59}. Homozygous EE individuals tend to reach sexual maturity earlier in life, whereas homozygous LL individuals tend to reach sexual maturity later; however, heterozygous males
reach sexual maturity earlier while heterozygous females reach sexual maturity later (see Figure 2b of Barson et al.\textsuperscript{59}). There is evidence for sex-specific fitness optima in age at sexual maturity in these salmon, which follows the typical expectation for sex differences along the slow-fast life history continuum: developing slowly results in larger body size at sexual maturity, which correlates more strongly to fitness in females; developing faster enables reaching sexual maturity earlier, which is typically more important for male fitness\textsuperscript{59,153,179–182}. The example is analogous to Fig. 1B, but without knowing the shape of the fitness landscape (Fig. 1C-E) we can neither predict the total fitness for the three genotypes, nor \textit{vice versa}\textsuperscript{59}. Still, their results provide very strong evidence that trait-level sex-specific dominance reversal has likely assisted sexually antagonistic selection in maintaining genetic variation at the \textit{VGLL3} locus\textsuperscript{59}.

Johnston et al.’s\textsuperscript{46} study of wild Soay sheep (\textit{Ovis aries}) emphasizes the role of overdominance as well as life history tradeoffs, but not dominance reversal, \textit{per se} (Table 1). However, the point estimates of \textit{RXFP2}’s allelic effects on male reproductive success and male survival appear to exhibit a beneficial reversal of dominance that is plausibly the cause of the inferred overdominance for fitness at that locus\textsuperscript{46}. Homozygous \textit{Ho\textsuperscript{+}Ho\textsuperscript{+}} males have relatively high reproductive success but low survival, and \textit{Ho\textsuperscript{P}Ho\textsuperscript{P}} males vice versa, while heterozygotes (\textit{Ho\textsuperscript{+}Ho\textsuperscript{P}}) have nearly equal male reproductive success to \textit{Ho\textsuperscript{+}Ho\textsuperscript{+}} homozygotes and nearly equal survival to \textit{Ho\textsuperscript{P}Ho\textsuperscript{P}} homozygotes (see Figure 2a versus 2b of Johnston et al.\textsuperscript{46}). The combination of these life history traits yields overdominance for fitness (see Figure 2c of Johnston et al. 2013), which can occur when the tradeoff is between individual fitness components that combine to determine total fitness, even when overdominance within each fitness component is not allowed\textsuperscript{21}. Although we do not show dominance reversals between fitness components, \textit{per se}, in Fig. 1, one can intuit the consequence of the shape of the fitness landscape (Fig 1C-E) in determining the presence/absence or magnitude of overdominance that would manifest by extrapolating the results of Fig. 1ii,iv,vi to a scenario in which fitness components combine to determine individuals’ total fitness: the likelihood of overdominance would be Fig. 1D > Fig. 1C > Fig. 1E. \textit{RXFP2}’s overdominance for fitness was
the focus of Johnston et al.’s study, but the inferred overdominance appears to be due to dominance-reversed allelic effects on survival and reproductive success.

In another example of a survival/reproduction tradeoff, Jardine et al. identify antagonistic pleiotropic effects on the classic and well-known fruitless (fru) gene in D. melanogaster (Table 1). They first identified a 1 kb region of elevated nucleotide diversity and Tajima’s D using population genomic data from wild flies caught in the United States and Zambia, and then narrowed that down to a 400 bp polymorphic indel with short and long fru alleles, “S” and “L”, respectively. We caution that one of the homozygous genotypes (L/L) that would be most desirable for discussing dominance reversal is not available due to details of the creation of their allelic lines. While the heterozygous effects (L/S) are able to be contrasted to the S/S homozygous genotype, they are only able to be contrasted to the effect of the L allele in its isolated, hemizygous confirmation (i.e., L/-), where the non-focal homologue carries a deficiency (a deletion) covering the fru gene. One might speculate that, if anything, the fru deficiency is more similar to the S allele (which carries the 400 bp deletion, see above), which would make the L/- genotype similar to a L/S heterozygote instead, but their results speak to the contrary – the L/- genotype is more consistent with an “isolated L allele” interpretation. Point estimates from laboratory fitness assays averaged over three different genetic backgrounds revealed that the S allele (in both the S/S and S/- arrangement) conferred greater male mating success but lower larval survival than the L allele (in its L/- arrangement) (see Figure 2b and Figure 3, respectively, of Jardine et al.). Heterozygous L/S flies tended to have equally high male mating success to S/S (as well as S/-) flies, but also equally high larval survival to L/- flies (see Figure 2b and Figure 3, respectively, of Jardine et al.). Hence the beneficial allele for each trait of this fru indel is dominant for that trait expression in heterozygotes. As with the previous example, this could generate overdominance since these alternative contexts are actually components of individual fitness, perhaps depending on the shape of the fitness landscape (Fig. 1; see previous paragraph).

Fittingly, their method for identifying this indel was via a genome scan for signatures of balancing selection, which would be more evident/detectable for overdominant balanced polymorphisms than for antagonistic
balanced polymorphisms that are not overdominant (see *A Primer on Antagonistic Pleiotropy*, above). What is perhaps missing from that understanding, which Jardine et al.’s evidence speaks to, is that those more detectable overdominant polymorphisms could be dominance reversed antagonistic polymorphisms with pleiotropic effects on individual fitness components.

Pearse et al. and Mérot et al. both identified dominance reversal in major-effect autosomal inversion polymorphisms that underlie life history traits with sex-specific fitness optima (Table 1). Both examples involve the interplay between life history tradeoffs, environmental effects, and sex- or trait-specific dominance reversals combining to consequently maintain polymorphism for these fitness-determining inversions. Pearse et al. investigated a large double-inverted supergene (Omy05) in the rainbow trout, *Oncorhynchus mykiss*, where the ancestral and rearranged alleles underlie variation in an environmentally-mediated reproductive strategy with sexually antagonistic effects on fitness. They found the statistical model of best fit to explain their capture-recapture data was one that included a sex-specific dominance term (see Figure 3 of Pearse et al.). Their findings ultimately suggest that dominance reversal has assisted the maintenance of this major-effect sexually antagonistic polymorphism for ~1.5 million years. Similarly, Mérot et al. studied a large inversion is in the seaweed fly, *Coelopa frigida*, whose allelic effects represent a survival/reproduction tradeoff resulting in overdominance. Their experimental evolution data suggest that the overdominance emerges due to varying strengths and directions of dominance effects between life history traits and sexes (see Figure 2 of Mérot et al.). Their numerical simulations suggest that dominance reversal between survival and reproduction would generate levels of overdominance that are consistent with empirical observations (see Figure 5 of Mérot et al.). Both of these studies shed light on the potential complexity of antagonistic pleiotropy, and hence its elusiveness. These examples relate to theory showing that mere sex-differences in the strength, but not direction, of selection acting on alternative alleles for loci underlying different fitness components can generate overall antagonistic effects on fitness. Mérot et al. add a layer of complexity to this theory, namely, that dominance-reversed fitness components may interact with multivariate selection to further
facilitate the maintenance of polymorphisms for fitness via antagonistic pleiotropy, which they show could potentially result in overdominance for fitness (akin to previous examples). None of that is particularly surprising in principle, since both multivariate sex-differences in the strength of selection\textsuperscript{99} and dominance reversals (Box 1) can, alone, assist the stable maintenance of genetic variation – and result in overdominance when the tradeoff is between fitness components\textsuperscript{21} – but Mérot et al.’s\textsuperscript{147} study gives precedent to the intuition that these effects can work in concert to maintain genetic variation for fitness.

*Polygenic evidence*

Posavi et al.\textsuperscript{52} deliberately set out to investigate dominance reversal between saltwater and freshwater environments in the invasive copepod *Eurytemora affinis* (Table 1). They derived two inbred strains from each of two salinity environments, saltwater and freshwater, and crossed them in a sex-specific full diallel cross\textsuperscript{104} to compare survival of within- versus between-salinity F\textsubscript{1} offspring in each salinity environments\textsuperscript{52}. These crosses yield 16 combinations: four within-strain inbred ‘selfs’, four within-salinity between-strain crosses, and eight between-salinity crosses (see Table 1 of Posavi et al.\textsuperscript{52}). Note that because the two inbred strains from a given salinity represent independent genetic backgrounds from their respective populations, the offspring of within-salinity crosses will be homozygous for loci that are likely important for adaptation to local salinity levels but mostly heterozygous elsewhere in the genome (as opposed to within-strain selfs), providing a like-to-like comparison of within- versus between-salinity crosses that is not confounded by the effects of background levels of heterozygosity or hybrid vigor\textsuperscript{52}. All eight between-salinity crosses that were presumably heterozygous for salinity-adaptation loci exhibited equally high probabilities of survival to that of the four within-salinity crosses in their ‘correct’ salinities, whereas those same four within-salinity crosses exhibited substantially lower probabilities of survival in their ‘wrong’ salinities (see orange and blue dashed lines/bars compared to all purple lines/bars (at 0 versus 15 PSU) of Figures 3,4,5 of Posavi et al.\textsuperscript{52}). Assuming high- and low-salinity adaptation in this system
is largely governed by the same loci (rather than separate loci encoding high- versus low-salinity survival), this evidence is consistent with dominance reversals maintaining genetic variation under niche-antagonism, where the salinity-adaptation heterozygotes (i.e., the between-salinity crosses) exhibit high survival in both high- and low-salinity niches, potentially representing any of the scenarios depicted in Fig. 1ii, iii, iv, or even vi.

In another diallel study, Grieshop and Arnqvist\textsuperscript{72} provided the first evidence of sex-specific dominance reversal for fitness, \textit{per se} (Table 1). They used 16 inbred strains from a wild-caught population of seed beetle (\textit{Callosobruchus maculatus}) that is known to harbor abundant sexually antagonistic genetic variation for fitness\textsuperscript{58,153}. Their full diallel cross\textsuperscript{104} generated \(\sim 240\) unique outbred \(F_1\) combinations and 16 within-strain \(F_1\) selfs, for which they obtained replicated estimates of sex-specific competitive lifetime reproductive success (i.e., fitness). Their quantitative genetic analysis revealed that dominance and sex-specific dominance were the largest components of variance in fitness for this population\textsuperscript{72}. However, it was their novel extension of Hayman's\textsuperscript{187} array covariances\textsuperscript{104} that enabled them to provide an estimate of how dominant each of the 16 strains' fixed allelic variation was relative to one another's (see Supporting Information S2 for details of this \textit{Dominance ordination} method\textsuperscript{72}). This was done in \(F_1\) males and females separately, where the null expectation was that the relative dominance/recessive ordination among strains should be the same regardless of the sex in which it is measured\textsuperscript{72} (S2). In contrast to the null prediction, they found that strains whose fixed genetic variation tended to be dominant to that of other strains in one sex was recessive to that of other strains when measured in the opposite sex (see Figure 3A,B of Grieshop and Arnqvist\textsuperscript{72}). In other words, the allelic variants for fitness in their population were overwhelmingly dominant in one sex but recessive in the other\textsuperscript{72}. Their findings (reviewed by Connallon and Chenoweth\textsuperscript{118}) represent a polygenic signal of sex-specific dominance reversal that is the likely cause of this population's abundant sexually antagonistic genetic variance in fitness\textsuperscript{58,72,153}. It is unclear whether the loci underlying Grieshop and Arnqvist's\textsuperscript{72} results reflect the scenario depicted in Fig 1ii,iii,iv or some mixture those. Regardless of the mechanism, such a polygenic phenomenon of sex-specific dominance reversal for fitness
could be responsible for Ruzicka et al.’s finding that hundreds of sexually antagonistic polymorphisms throughout the *D. melanogaster* genome have been maintained for ~1 million years (see *A Primer on Antagonistic Pleiotropy*).

A study by Le Poul et al. straddles the polygenic/major-effect loci boundary, as they investigated the individual genes lying within a super gene that make up a mimicry polymorphism with important fitness consequences in the butterfly *Heliconius numata* (Table 1). They aimed to assess whether measures of intermediate dominance coefficients for overall wing color pattern was attributable to “mosaic dominance” – a term commonly used in the study of color pattern inheritance that was originally defined by Tan, where heterozygotes exhibit the darker pigment on any part that is darker in one or the other parental homozygotes. It is interesting to note that this term emerged long before the debates over dominance reversal gained speed, and it seems to have persisted outside of those debates. Regardless, color hierarchies (e.g., black dominant to orange, orange dominant to white) can generate dominance reversals between color patches (as in Figure 4 of Gautier et al.). Much of Le Poul et al.’s evidence points to dominance relationships between alleles being reversed between different patches of wing color. All eight within-population allele-pairs studied show opposite parental alleles being dominant for different color patches (traits) in F₁ offspring (see Figure 2 of Le Poul et al., in which all “Dominance heatmaps” have both red and blue). Perhaps the clearest case of dominance reversal between color patches is between the *tar* and *arc* alleles, where the *tar* allele is dominant to the *arc* allele with respect to its large black patch but recessive with respect to its white patch (Figure 2g of Le Poul et al.). Note also that not all darker-pigmented areas are necessarily dominant, as Tan had originally hypothesized (e.g., Figure 2d,e of Le Poul et al. show some regions of orange being dominant to black). As with other examples above, Le Poul et al.’s evidence of dominance reversal between individual traits could, in principle, add up to overdominance for fitness. Regardless, these opposite dominance relationships underlying color pattern variation likely assist the stable maintenance of a widespread and persistent mimicry polymorphism by limiting the production of intermediate, non-mimetic individuals.
As our last example, Chen et al.\textsuperscript{159} compared gene expression between two unique inbred strains of \textit{D. melanogaster} and their F\textsubscript{1} hybrids between alternative hot or cold temperatures. Having both hot- and cold-reared F\textsubscript{1}s enabled them to identify genes whose parental alleles were inferred to be oppositely dominant/recessive to one another in opposite temperature environments\textsuperscript{159}. Their method looked at the fold-difference of each gene’s expression level in one inbred parent strain relative to the F\textsubscript{1} hybrid and contrasted this measure with that of the other inbred parent in order to determine which parental strain’s allele was dominant over the other’s\textsuperscript{159}. They identified 1,384 genes in which the opposite parental strain allele was dominant in hot versus cold environments, which they referred to as “dominance swapped”\textsuperscript{159}. However, their study was not intended to reveal dominance reversals, \textit{per se}, and as such their analysis leaves room for alternative explanations. Namely, background genetic differences between parental genomes could influence differences in their relative expression compared to hybrids. In the Supporting Information (S2) we describe an alternative analysis of allele-specific expression data that circumvents this caveat by simply comparing allelic imbalance\textsuperscript{144} in the F\textsubscript{1} hybrids between alternative contexts, thereby standardizing all background genetic effects. By this method (S2), allele-specific expression data can identify genes with reversed patterns of allelic imbalance\textsuperscript{144} between contexts. We have demonstrated that reversed allelic imbalance between contexts is a possible outcome for transcription factors under antagonistic selection (Box 2, S1). Fittingly, Chen et al.\textsuperscript{159} found enrichment among their dominance-swapped genes – some of which likely do represent dominance reversals – for 13 different transcription factor binding sites, many featuring binding sites for multiple transcription factors. For example, 934 of their dominance-swapped genes featured a common pair of transcription factor binding sites (\textit{Chro} and \textit{BEAF-32}). Two of the 13 transcription factors showing enrichment among the dominance-swapped genes were themselves dominance-swapped\textsuperscript{159}. One transcription factor (\textit{mip120}) was particularly interesting in light of our biophysically explicit model of a dominance modifier (Box 2, S1), because it exhibited \textit{cis}-regulatory variation in the hot environment but both \textit{cis}- and \textit{trans}-regulatory variation\textsuperscript{144} in the cold environment\textsuperscript{159}. This is vaguely consistent, albeit speculative, with our model (Box 2, S1) in that one allele
could be generally dominant (e.g., owing to its superior binding affinity) and thereby generate cis-
regulatory variation in both environments, while the other allele could achieve cold-specific dominance via
increased cold-environment concentration (e.g., via a an up-stream environmentally dependent trans-
acting regulatory stimulus) – which could generate cis-by-trans variation.

**Additional considerations**

Dominance reversal can distort the detection of antagonistic genetic variation by conventional methods. As
mentioned, antagonistic sites in the genome will generate very weak, likely undetectable patterns of
balancing selection relative to overdominant sites\(^7\). Dominance reversal actually slightly increases the
signature of balancing selection generated by antagonistic polymorphisms\(^7\). However, since dominance
reversal between individual-level fitness components can result in overdominance for total fitness\(^21,46,147\),
and since overdominant loci generate a much more detectable signature of balancing selection than
antagonistic sites (even if dominance reversed)\(^7\), dominance reversal may bias genome scans toward
detecting antagonistic pleiotropy between individual-level fitness components\(^21-23\) as opposed to between
niches, time points, environments, or sexes\(^15,18,20,28,32,33\). As a speculative example, it is possible that the
dominance reversal between larval survival and mating success in the fru indel of Jardine et al.\(^178\)
(reviewed above) causes it to be overdominant for fitness (as in\(^46\), reviewed above), which is perhaps why
it exhibits a detectable signature of balancing selection (elevated nucleotide diversity and Tajima’s D).
Thus, while dominance reversals may slightly improve the detectability of antagonistic balancing selection
via genome scans, it may impose a bias in favor of detecting life history tradeoffs relative to other forms of
antagonistic selection.

There is also interest in using \(F_{ST}\) to identify regions of the genome that have divergent allele
frequencies owing to antagonistic selection. This method has very low power to detect sexually
antagonistic viability selection through \(F_{ST}\) differentiation between the adult males and females of a given
Dominance reversal makes this even worse (see Figure 4B of Kasimatis et al.95). There is likewise very low power to detect temporally antagonistic selection by this method190, and that is also made worse by dominance reversal119,120. Specifically, because dominance reversal offers the most drastic stabilizing effect to weakly selected antagonistic polymorphisms (Box 1), a polygenic model of temporally antagonistic selection predicts that weak-effect polymorphisms will be disproportionately maintained, so much so that under certain conditions no antagonistic polymorphisms of detectable effect-size will be maintained119,120. It is possible, if speculative, that such a process could be at least partly responsible for causing false-positive discoveries of temporally antagonistic selection via $F_{ST}$ scans (see S6 and Figure S3 of Buffalo and Coop190) since dominance reversal may cause the only true-positive antagonistic polymorphisms to be of undetectably small effect-size119,120.

In principle, dominance reversals could also affect the ability to detect antagonistic polymorphisms in genome-wide association studies (GWAS) due to the explicit assumption of additive genetic effects. This may seem contradictory to the fact that antagonistic selection should generate a greater contribution to additive genetic variance6,26,79 (see A primer on antagonistic pleiotropy), but we caution that the connection between quantitative genetic variance components and the underlying molecular genetic phenomena that influence them is not straightforward191. Moreover, details in the methodology could determine whether or not dominance reversals will affect the estimated associations. For example, Ruzicka et al.’s60 genome-wide association study (see Introduction) employed a specific technique available in D. melanogaster – the LH$_M$ hemi-clone generator – that enhances the ability to detect additive genetic effects. Whether this and other methodological details in GWAS help or hurt the ability to detect antagonistic polymorphisms when dominance reversal is at play is currently unclear, but could be determined theoretically.

The theoretical and empirical data reviewed in this article argue that segregating antagonistic genetic variation should be enriched for beneficial reversals of dominance. Thus, methods that focus on detecting signatures of dominance reversal may represent a superior, or perhaps complementary, approach to traditional methods of identifying antagonistic genetic variation. Two methods seem
particularly promising in this regard: dominance ordination and allele-specific expression. Both are explained in detail in the Supporting Information (S2), and there is ample scope for further development in both. Briefly, dominance ordination is currently best utilized for its ability to reveal a quantitative genetic signature of dominance reversal in full diallel data and/or to place some feasible number of strains (perhaps ≤ 20) in order along a derived axis of dominance reversal (S2). Research is needed to explore whether dominance ordination may be extended to more feasible or common types of data such as partial diallels, other breeding designs, and pedigree data. As far as its ability to reveal patterns of dominance reversal in the genome, further research is needed to explore more direct approaches such as conducting the dominance ordination at the chromosomal- or linkage-block-level rather than among genetic strains (S2). By contrast, the allele-specific expression approach is capable of identifying specific dominance-reversed sites in the genome (S2), but immediately restricts the investigation to protein coding sites. That said, follow-up analyses could employ ATAC-seq (or similar methods) to potentially reveal non-coding components of the regulatory networks that surround a candidate list of genes showing reversed allelic imbalance between contexts (S2). Lastly, single-cell isolation (cell-sorting) technologies could be integrated with this allele-specific expression method (S2) to identify reversed patterns of allelic imbalance between a variety of tissue and cell types.

We have reviewed the history, theory and data surrounding the role of beneficial reversals of dominance resolving genetic conflicts, maintaining genetic variation and promoting local adaptation. The dismissal of beneficial reversals of dominance has hindered our understanding of the role of antagonistic selection in evolution and its detection in the genome. We hope this article spawns new research in these areas.
## Definitions

| Term                                | Definition                                                                                                                                 |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Additivity                          | Sign and magnitude of allelic effects simply add up both within and between loci to a cumulative effect.                                    |
| Antagonistic pleiotropy             | Fitness effects of alleles at a given locus have opposite sign in opposite contexts.                                                    |
| Balancing selection                 | A scenario in which alternative alleles of a given locus are actively maintained by selection.                                          |
| Beneficial reversals of dominance   | Heterozygote at locus under antagonistic pleiotropy exhibit above-average fitness relative to the two homozygous genotypes in each context (Fig. 1, Box 1). |
| Dominance modifier                  | Any allele, combination of alleles or epigenetic process that can affect the dominance properties of alleles at another locus (Box 2).       |
| Genetic conflict                    | The segregation/genetic load imposed by antagonistic polymorphisms (Box 3).                                                               |
| Mutation-selection balance          | When genetic variance owes to incoming mutant alleles and selection against their deleterious effects, typically across many loci.        |
| Resolution (of genetic conflict)    | When the reduced context-specific (and hence population mean) fitness owing to loci under antagonistic pleiotropy is somehow mitigated, enabling at least partly rescued fitness (Box 3). |
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Author Contributions

KG and KRK conceived of the article. KG did the literature search. KG and EKHH conducted the novel theory presented in Box 2 and S1 – EKHH is solely responsible for the Python coding of the biophysical models of gene regulation. KG wrote the original draft of the manuscript including the underlying R code for Fig 1. All authors contributed to editing the manuscript.

Data Archiving

The underlying Python code (for Box 2, S1) and R code (for Fig 1) are available upon request, and will be uploaded to an appropriate repository upon publication.
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Supporting Information:

Dominance reversals, antagonistic pleiotropy, and the maintenance of genetic variation

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S1. Simulating the evolution of biophysically explicit dominance modifiers

S1. Methods

Our simulation model builds off of Porter et al.\textsuperscript{143} and is based on the premise that transcription factors (TF) and binding sites behave according to the thermodynamic and kinetic properties of molecular interactions. The proportion of time that a binding site is occupied by a TF molecule (fractional occupancy) determines gene expression levels. For a generic diploid locus where TF variants $T_1$ and $T_2$ compete for occupancy at promotor (or repressor) sites $P_1$ and $P_2$, we utilize equation (2a) from Porter et al.\textsuperscript{143} to define the fractional occupancy of $T_1$ on $P_1$ as:

$$F([T_1], [T_2], m_{11}, m_{21}, k) = \frac{[T_1]}{1 + \frac{[T_1]}{m_{11}} + \frac{[T_2]}{m_{21}}}.$$  \hspace{1cm} (1.1)

The square brackets denote the concentration of the TF, e.g., $[T_1]$ represents the concentration of $T_1$. $m_{11}$ represents the proportion of mismatched bits between $T_1$ and $P_1$, $m_{21}$ presents the proportion of mismatched bits between $T_2$ and $P_1$. Lastly, $k$ represents the stepwise change in the dissociation constant\textsuperscript{143}.

Our diploid model consists of two unlinked interacting genes A and B (Figure S1.1, Table S1.1). Our model is likely an appropriate simplification of reality: while real gene regulation may be considerably more complicated at a minimum\textsuperscript{196}, that may be largely due to molecular redundancies owing to the evolutionary entrenchment of gene networks down paths of no return\textsuperscript{197}. We will use the subscript $i = \{1, 2\}$ to represent the homolog to which the gene belongs. Gene A contains a \textit{cis}-regulatory binding site represented by $\alpha_i$ which possesses 11 allelic variants with values between 0 and 1 in 0.1 increments; $\alpha_i = \{0, 0.1, ..., 0.9, 1\}$. This mimics the 11 different functional alleles that are possible for a typical eukaryotic transcription factor binding site – from all 10 nucleotides matching to none matching\textsuperscript{198}. Gene A also contains a bi-allelic coding region with variants $A_i = \{1, 2\}$, which expresses a TF that regulates the
expression of Gene B. Importantly, the TF expressed by allele $A_i = 1$ ultimately downregulates the expression of Gene B, while the TF expressed by allele $A_i = 2$ ultimately upregulates the expression of Gene B (see equation (2.6), below). Expression of $A_i$ ([$A_i$]) is controlled by the binding of an anticorrelated, sex-limited, regulatory stimulus, $D$, onto the binding site $\alpha_i$. This sex-limited regulatory stimulus could be thought of as approximating a sex-limited hormone, or alternatively spliced dsx or fru genes in insects\textsuperscript{145}.

The fractional occupancy of $D$, onto the binding site $\alpha_i$ depends on its concentration, [$D$], the proportion of mismatched bits, $m_{Da}$, and the stepwise change in the dissociation constant $k_\alpha$ (Porter et al.\textsuperscript{143}). Importantly, $m_{Da}$ depends on the sex of the individual and the allelic variant of $\alpha_i$. The male version of the regulatory stimuli, $D$, binds optimally to allele $\alpha_i = 0$, and the female version of $D$ binds optimally to allele $\alpha_i = 1$:

$$m_{Da}(\text{sex, } \alpha_i) = \begin{cases} 
\alpha_i, & \text{sex = male} \\
1 - \alpha_i, & \text{sex = female}
\end{cases} \quad (1.2)$$

Thus, [$A_i$] is the product of the fractional occupancy and $G_A$, which represents the maximum concentration that can be achieved, so that the concentration of $A_1$ and $A_2$ is calculated as follows (Figure S1.1, Table S1.1):

$$[A_1] = G_A \times \left( \frac{[D]/k_\alpha m_{Da}(\text{sex, } \alpha_1)}{1 + 2[D]/k_\alpha m_{Da}(\text{sex, } \alpha_1)} \right), \quad (1.3)$$

$$[A_2] = G_A \times \left( \frac{[D]/k_\alpha m_{Da}(\text{sex, } \alpha_2)}{1 + 2[D]/k_\alpha m_{Da}(\text{sex, } \alpha_2)} \right). \quad (1.4)$$
Fig S1.1: Cartoon schematic of some of the parameters defined in Table S1.1. Due to the sex-specific fitness optima for \( \varphi \) (the standardized expression of Gene B, \([B]\), see below), and the fact that \( A_i = 1 \) and \( A_i = 2 \) affect \([B]\) in opposite directions, \( A_i = 1 \) and \( A_i = 2 \) represent the male- and female-benefit alleles, respectively, of the focal sexually antagonistic polymorphism at \( A_i \). \( D \), \( A \) and \( B \) are unlinked, whereas the protein-coding sites of Genes A and B, \( A_i \) and \( B_i \), are linked to their respective cis-regulatory binding sites, \( \alpha_i \) and \( \beta_i \).
| Parameter | Definition |
|-----------|------------|
| $i$ | Index for homolog; $i = \{1, 2\}$. |
| $\alpha_i$ | Allelic state of $\alpha$ at homologue $i$; $\alpha_i = \{0, 0.1, ..., 0.9, 1\}$. |
| $A_i$ | Allelic state of $A$ at homologue $i$; $A_i = 1$ reduces $[B]$, and $A_i = 2$ elevates $[B]$. |
| $\beta_i$ | Allelic state of $\beta$ at homologue $i$; $\beta_i = \{0, 0.1, ..., 0.9, 1\}$. |
| $m_{D\alpha}(\text{sex}, \alpha_i)$ | Proportion of mismatched bits between $D$ and $\alpha_i$ as a function of sex and $\alpha_i$. |
| $m_{A\beta}(A_i, \beta_i)$ | Proportion of mismatched bits between $A_i$ and $\beta_i$. |
| $k_\alpha$ | Stepwise change in the dissociation constant for $D$ binding to $\alpha_i$. |
| $k_\beta$ | Stepwise change in the dissociation constant for $A_i$ binding to $\beta_i$. |
| $G_A$ | Concentration for protein of allele $A_i$ if fractional occupancy at binding site is 1. $G_A \leq [A_{\text{sat}}]$. |
| $H(A_i)$ | Effect of $A_i$ on $[B]$; $H(A_i) = \begin{cases} -1, & A_i = 1 \\ +1, & A_i = 2 \end{cases}$. |
| $[D]$ | Concentration of sex-limited regulatory stimulus. |
| $[A_i]$ | Concentration of protein expressed by $A_i$. |
| $[B]$ | Concentration (expression level) of protein expressed by $B$. |
| $Z$ | Baseline $[B]$. |
| $[A_{\text{sat}}]$ | $[A_i]$ that would saturate binding sites of $B$; determines $[B_{\text{min}}]$ and $[B_{\text{max}}]$. |
| $[B_{\text{min}}]$ | $[B]$ when saturated by $A_i = 1$, which reduces expression. |
| $[B_{\text{max}}]$ | $[B]$ when saturated by $A_2 = 2$, which elevates expression. |
| $\varphi$ | Standardized $[B]$. |
| $s_m, s_f$ | Selection coefficient for males and females, respectively. |
| $\gamma_m, \gamma_f$ | Fitness curvature for males and females, respectively. |
| $W_m(\varphi), W_f(\varphi)$ | Absolute fitness for males and females, respectively. |
Gene B contains a cis-regulatory binding site represented by $\beta_i$ which possesses 11 allelic variants ($\beta_i = \{0, 0.1, …, 0.9, 1\}$) and a monomorphic coding region from which the expression level, $[B]$, ultimately determines the fitness of the individual. The fractional occupancy of the TF expressed by $A_i$, onto the binding site $\beta_i$ depends on its concentration, $[A_i]$, the proportion of mismatched bits, $m_{A\beta}$, and the stepwise change in the dissociation constant $k_\beta$. $m_{A\beta}$ depends on the allelic state of both $A_i$ and $\beta_i$, such that allele $A_i = 1$ binds optimally to allele $\beta_i = 0$, and allele $A_i = 2$ binds optimally to allele $\beta_i = 1$:

$$m_{A\beta}(A_i, \beta_i) = \begin{cases} \beta_i, & A_i = 1 \\ 1 - \beta_i, & A_i = 2 \end{cases} \quad (1.5)$$

The expression level of Gene B, $[B]$, is determined by the combination of all four possible allele-specific interactions between $[A_i]$ and $\beta_i$ like so:

$$[B] = Z + \frac{1}{2} \left( F([A_1], [A_2], m_{A\beta}(A_1, \beta_1), m_{A\beta}(A_2, \beta_1), k_\beta)H(A_1) + F([A_2], [A_1], m_{A\beta}(A_2, \beta_1), m_{A\beta}(A_1, \beta_1), k_\beta)H(A_2) + F([A_1], [A_2], m_{A\beta}(A_1, \beta_2), m_{A\beta}(A_2, \beta_2), k_\beta)H(A_1) + F([A_2], [A_2], m_{A\beta}(A_2, \beta_2), m_{A\beta}(A_1, \beta_2), k_\beta)H(A_2) \right),$$

$$H(A_i) = \begin{cases} -1, & A_i = 1 \\ +1, & A_i = 2 \end{cases} \quad (1.6)$$

where $Z$ represents the base line expression level of Gene B, and $H$ scales the direction of the allele-specific effects of $A_i$ on $[B]$ such that $A_i = 1$ downregulates and $A_i = 2$ upregulates. When an individual is homozygous at the $A_i$ locus (i.e., $A_1 = A_2$), the first two terms in equation 1.6 become equivalent and the last two terms in equation 1.6 also become equivalent. We normalize $[B]$ to the range $[0, 1]$ using:

$$\varphi = \frac{[B] - [B_{min}]}{[B_{max}] - [B_{min}]} \quad (1.7)$$

The minimum $[B]$ occurs when $A_1 = A_2 = 1$, $[A_1] + [A_2] = [A_{sat}]$ (see Table S1.1), and $\beta_i = 0$ to yield $[B_{min}] = Z - [A_{sat}]/(1 + [A_{sat}])$. The maximum $[B]$ occurs when $A_1 = A_2 = 2$, $[A_1] + [A_2] = [A_{sat}]$, and $\beta_i = 1$ to yield $[B_{max}] = Z + [A_{sat}]/(1 + [A_{sat}])$. 
Male- and female-specific fitness as a function of the normalized expression, $\varphi$, is represented by $W_m(\varphi)$ and $W_f(\varphi)$, respectively, calculated as

$$W_m(\varphi) = 1 - (s_m \varphi)^{\gamma_m}$$

and

$$W_f(\varphi) = 1 - (s(1 - \varphi))^{\gamma_f},$$

where $s_m$ and $s_f$ are the sex-specific selection coefficients, and $\gamma_m$ and $\gamma_f$ control the curvature of the fitness landscape for each sex (e.g., $\gamma_m = 1$ for linear/additive fitness effects). The opposite sign of sex-specific fitness consequences for $\varphi$ represents sex-specific fitness optima, and because alternative alleles $A_i = 1$ and $A_i = 2$ affect $\varphi$ in opposite directions (via their effects on $[B]$, see equation (1.6) and Table S1.1), they respectively represent the focal male- and female-benefit alleles of a sexually antagonistic polymorphism (Fig S1.1).

We used simulations to assess whether this model can maintain polymorphism at $A_i$. All simulations consisted of 5,000 male and 5,000 female individuals, and ran for 50,000 non-overlapping generations. Individuals began with alleles at $A_i$, $\alpha_i$, and $\beta_i$ selected randomly from a uniform distribution; recall that $A_i$ can have values $\{1, 2\}$, while $\alpha_i$ and $\beta_i$ can have values $\{0, 0.1, 0.2, ..., 0.9, 1\}$. Every generation, each of the 10,000 offspring were produced as follows. A potential female parent is chosen randomly and their fitness relative to the maximum among females, $W_f(\varphi) / W_{f,\text{max}}$, was compared to a uniform random deviate (Uniform $[0, 1]$), where $W_{f,\text{max}}$ is the largest value of $W_f(\varphi)$ in the population. The female was kept if their relative fitness surpasses the uniform random deviate, otherwise, the process was repeated until a suitable female was chosen. A male was chosen using the same procedure. Gametes from each parent were produced following segregation between the unlinked Genes A and B. After combining the two gametes from the parents, the alleles at $\alpha_i$ and $\beta_i$ had a probability $\mu_\alpha$ and $\mu_\beta$, respectively, of mutating to an adjacent value. If $\alpha_i$ or $\beta_i$ has allelic value 0 then it could only mutate to 0.1 and analogously, if $\alpha_i$ or $\beta_i$ has
allelic value 1 then it could only mutate to 0.9. Finally, 5,000 offspring were randomly assigned to be females and the remaining 5,000 assigned to be males.

We present simulations run with a range of selection coefficients, $s_f = s_m = \{0.005, 0.01, 0.02, 0.05\}$. We ran all simulations under a linear fitness landscape, $\gamma_f = \gamma_m = 1$, as we were interested in whether this gene regulatory network could adaptively evolve to constitute a sex-specific "dominance modifier" that resolves genetic conflict and protects the focal polymorphisms from becoming fixed without additional beneficial reversal of dominance stemming from the concavity of the fitness landscape. One set of simulations allowed both cis-regulatory binding sites on Gene A and B ($\alpha_i$ and $\beta_i$) to mutate with rates $\mu_{\alpha} = \mu_{\beta} = 0.005$. Another set of simulations only allowed only $\alpha_i$ to mutate with $\mu_{\alpha} = 0.005$ and fixed the value of $\beta_i$ at 0.5 for all individuals ($\mu_{\beta} = 0$). The contrast between simulations that allow $\beta_i$ to mutate/evolve and those that do not serves as an approximation of the role of the epistatic interaction between Genes A and B in influencing the evolution and signature of the sex-specific dominance modifier, while keeping all else equal. Each parameter set was replicated 100 times and the data from the last generation (i.e., 50,000) was used for analysis.

We focus our analysis on the polymorphism at the bi-allelic coding region of Gene A. Since $A_i$ does not undergo mutation, simulations either end with the population having maintained polymorphism at $A_i$ or fixed for one of the two alleles $A_i = 1$ or $A_i = 2$. Signatures used to assess whether the polymorphism at $A_i$ was maintained by sexually antagonistic selection (as opposed to drift) included: the presence of beneficial reversals of dominance for fitness between alternative alleles at $A_i$, the relative abundance of high-fitness $\alpha_iA_i$ haplotypes, the average distance to the sex-specific fitness optima, and the sex-specific allelic imbalance at $A_i$. We considered there to be beneficial dominance reversal when the harmonic mean fitness of individuals heterozygous at the $A_i$ locus (genotype denoted as 1/2) is higher than the harmonic mean fitnesses of homozygous 1/1 genotypes and of homozygous 2/2 genotypes. We use the correlation between the allelic values at $\alpha_i$ and $A_i$ to gauge the presence of high-fitness $\alpha_iA_i$ haplotypes. A positive correlation suggests that allele $A_i = 1$ tend to be linked to $\alpha_i$ alleles with small values (i.e., male benefit
haplotypes) and that allele $A_i = 2$ tend to be linked to $\alpha_i$ alleles with large values (i.e., female benefit haplotypes). The average distance to the fitness optima for males was calculated as the normalized expression level of Gene B, $\phi$, averaged across all males. The average distance to fitness optima for females was calculated as 1 minus $\phi$, averaged across all females. Allelic imbalance for individuals heterozygous at the $A_i$ locus was calculated as the log$_2$ ratio of $[A_i = 2]$ to $[A_j = 1]$, such that positive values indicate the expression of allele $A_i = 2$ is higher than that for $A_i = 1$, and negative values indicate the opposite.

In addition, we interpret a unimodal distribution of $\alpha$ or $\beta$ alleles at the end state as representing the fixation of those sites, and bimodal distribution of $\alpha$ or $\beta$ alleles at the end state as representing maintenance of a functionally bi-allelic polymorphism. We anticipate that this would culminate in even more discrete, truly monomorphic or bi-allelic, equilibria under even more realistic parameter settings (namely, very low mutation rates and a very long number of generations). While the parameter settings for mutation rates in evolutionary simulations are typically arbitrary due to computational and time limits, we note that one consequence of setting a mutation rate for what is meant to reflect a 10-nucleotide sequence is that the per-nucleotide mutation rates that we are approximating are actually an order of magnitude lower than the value of our parameter setting. That is, to set $\mu_\alpha = 0.005$, for example, is to model a per-nucleotide mutation rate of 0.0005 for $\alpha$, since the mismatch $m_\beta \alpha$ of an allele at $\alpha_i$ approximates the total number of (mis)matched nucleotides in a binding site, which consists of 10 independently mutating nucleotides. This is only trivially important if/when considering the relationship between the strengths of mutation and selection upon interpreting our results.

**S1 Results**

Whether or not polymorphism at $A_i$ is maintained by the action of the surrounding gene regulatory phenomena is sensitive to the parameter settings chosen (Table S1.2, Fig S1.2). In general, $s_m$ and $s_f$ must
be sufficiently stronger than $\mu_\alpha$ (as well as $\mu_\beta$, when allowed) in order for selection to maintain the focal polymorphism at $A_i$.

Table S1.2. Proportion of simulations that ended with polymorphism at locus $A_i$.

| Selection strength | Binding site mutation rates | $\mu_\alpha = \mu_\beta = 0.005$ | $\mu_\alpha = 0.005, \mu_\beta = 0$ |
|--------------------|-----------------------------|----------------------------------|----------------------------------|
| 0.005              | 0.2                         | 0.16                             |                                  |
| 0.01               | 0.37                        | 0.25                             |                                  |
| 0.02               | 0.8                         | 0.65                             |                                  |
| 0.05               | 0.95                        | 0.99                             |                                  |
Fig S1.2: Proportion of 100 simulations maintaining polymorphism at $A_i$ for a range of selection strengths. Circles and triangles represent simulations in which $\beta_i$ was fixed and mutable, respectively.

Provided the focal polymorphism was maintained, three lines of reasoning suggest that it is due to the surrounding gene regulatory phenomena enabling selection to actively maintain it due to the ensuing dominance reversal partially resolving genetic conflict (see Box 2). First, the proportion of simulations that resulted in a beneficial reversal of dominance increased with increasing strength of selection (Fig S1.3). Second, there was typically a high prevalence of the most adaptive haplotypes relative to the non-adaptive haplotypes for Gene A, measured as a high correlation between the allelic values at $\alpha_i$ and $A_i$ (Fig S1.4). The positive correlation indicates that the male-benefit allele, $A_i = 1$, tends to be linked to $\alpha_i$ alleles with greater binding affinity to the male-limited regulatory stimulus, and that the female-benefit allele, $A_i = 2$,
tends to be linked with $\alpha_i$ alleles with a greater binding affinity to the female-limited regulatory stimulus. Third, the average distance of male and female individuals to their respective fitness optima was less than it would be for a simple codominant polymorphism (i.e., $< 0.5$) (Fig S1.5). This adaptive sex-specific dominance reversal yields a characteristic pattern of allele-specific expression akin to the findings of Chen et al.\textsuperscript{159} and Mishra et al. (unpublished), in which $A_i = 2$ is expressed higher than $A_i = 1$ in female heterozygotes (positive values of allelic imbalance), and \textit{vice versa} for male heterozygotes (Fig S1.6).
Fig S1.3. Beneficial reversals of dominance. Provided selection is sufficiently stronger than the mutation rate, beneficial reversals of dominance are an inevitable end state – perhaps even more likely when mutation/selection is allowed at $\beta_i$ for some strengths of selection, suggesting that epistatic interactions may be partly characteristic of sex-specific dominance modifiers. Circles and triangles represent simulations in which $\beta_i$ was fixed and mutable, respectively.
Fig S1.4: Adaptive haplotypes. Provided selection is sufficiently stronger than the mutation rate, selection acts to increase the frequency of adaptive haplotypes of Gene A, $\alpha_i A_i$ in both females (left) and male (right). For very weak strengths of selection ($s_f = s_m = 0.005$), this adaptive haplotype can arise more readily when $\beta_i$ is fixed. Each point represents the mean correlation (± bootstrap 95% CI) between allelic values of $A_i$ and $\alpha_i$, averaged across simulations that maintained polymorphism at $A_i$. Circles and triangles represent simulations in which $\beta_i$ was fixed and mutable, respectively.
Fig S1.5: Resolution of sexual conflict. Mean distance to fitness optima (± bootstrap 95% CI) for simulations where $A_i$ was polymorphic, fixed for the male-benefit allele ($A_i = 1$), or fixed for the female-benefit allele ($A_i = 2$). Distance to optima were averaged across simulations with different selection coefficients ($s_f = s_m = \{0.005, 0.01, 0.02, 0.05\}$). Females (left) and males (right) were less than halfway (< 0.5; dashed line) from their fitness optima, indicating partially resolved sexual conflict relative to a codominant polymorphism. Circles and triangles represent simulations in which $\beta_i$ was fixed and mutable, respectively.
Fig S1.6. **Reversed pattern of allelic imbalance points to sex-specific dominance modifier.** Each point represents the mean (± bootstrap 95% CI) \( \log_2 \) fold difference in expression between \( A_i = 2 \) and \( A_j = 1 \) alleles measured in female (left) and male (right) heterozygotes, average across simulations that maintained polymorphism at \( A_i \). The magnitude of the reversed allelic imbalance between the sexes increases with selection. Mutation at \( \beta_i \) may hinder detection by this method under particularly weak strengths of selection (\( s_f = s_m = 0.005 \)). Circles and triangles represent simulations in which \( \beta_i \) was fixed and mutable, respectively.

The effect of enabling some fitness variance to stem from an epistatic interaction between Genes A and B (approximated by enabling mutation/selection at \( \beta_i \)) was to increase the likelihood of maintaining the focal polymorphism (\( A_i \)) under \( s_f = s_m = \{0.01, 0.02\} \) (Fig S1.2), increase the likelihood of a beneficial reversal of dominance for fitness at \( A_i \) under \( s_f = s_m = \{0.005, 0.01, 0.02\} \) (Fig S1.3), reduce the ascent of beneficial haplotypes \( \alpha_i A_i \) under \( s_f = s_m = \{0.005\} \) (Fig S1.4), and reduce the magnitude of reversed allelic imbalance between the sexes under \( s_f = s_m = \{0.005\} \) (Fig S1.6).
Although we mostly focused on the polymorphism at $A_i$, we also observe qualitative differences in the distribution of the binding site alleles ($\alpha_i$ and $\beta_i$) between simulations that maintained polymorphism at $A_i$ and those that fixed for the male-benefit or the female-benefit allele of $A_i$ (Fig S1.7, S1.8). We observe a bimodal distribution of $\alpha_i$ when polymorphism was maintained at $A_i$ (Fig S1.7). In contrast, $\alpha_i$ was unimodal when $A_i$ ended up being fixed for $A_i = 1$ or $A_i = 2$. The distribution of $\alpha_i$ skewed towards smaller values when $A_i$ was fixed for the male-benefit allele and towards larger values when $A_i$ was fixed for the female-benefit allele. The pattern observed for the distributions of $\beta_i$ was similar but not as pronounced as that for $\alpha_i$ (Fig S1.8). Overall, this suggests that our gene-regulatory network under sexually-antagonistic selection not only maintains variation at the coding region $A_i$, but also for the binding sites $\alpha_i$ and $\beta_i$.

**Figure S1.7. Distribution of $\alpha_i$ alleles.** Simulations where $A_i$ was polymorphic (left), fixed for the male-benefit allele ($A_i = 1$) (middle), or fixed for the female-benefit allele ($A_i = 2$) (right) for simulations where $\beta$ was mutable. Only simulations under $s_f = s_m = \{0.02\}$ are shown. Each bar represents the mean frequency ($\pm$ bootstrap 95% CI) of $\alpha_i$ alleles, averaged across simulations.
Figure S1.8. Distribution of $\beta_i$ alleles. Simulations where $A_i$ was polymorphic (left), fixed for the male-benefit allele ($A_i = 1$) (middle), or fixed for the female-benefit allele ($A_i = 2$) (right) for simulations where $\beta$ was mutable. Only simulations under $s_f = s_m = 0.02$ are shown. Each bar represents the mean frequency ($\pm$ bootstrap 95% CI) of $\beta_i$ alleles, averaged across simulations.
S2. Methods of detecting dominance reversal in quantitative genetic and transcriptomic data

Dominance ordination

Grieshop and Arnqvist\textsuperscript{72} (see main text, Table 1) developed a quantitative genetic approach capable of revealing a polygenic signature of dominance reversal by subtly modifying a rarely used method first derived by Hayman\textsuperscript{187}. This new method was necessary because classical and advanced quantitative genetic partitioning of fitness variance, including estimating sex-/strain-specific dominance deviations, are insufficient at definitively revealing a signature of dominance reversal, largely due to the uncertainty in connecting population/molecular genetic phenomena to quantitative genetic metrics\textsuperscript{191}. Researchers conducting diallel crosses with the intention of assessing dominance reversals should decide prior to designing their experiment (1) whether dominance ordination is necessary for their question, (2) whether a diallel cross of sufficient size is feasible (see below).

A full diallel cross is a factorial cross among a panel of inbred strains\textsuperscript{104}. We will present an example in which the focal context is sex, hence, each cross (and reciprocal cross, see below) produces $F_1$ offspring in both contexts: male (sons) and female (daughters). The full diallel matrix includes a column and row for each of the inbred parental strains 1 through $n$, such that there are $n^2$ cells in the matrix. Some steps below require the full matrix (all data) to be considered at once, and other steps require splitting the data into their context-specific matrices (i.e., separating the ‘sons’ and ‘daughters’ data). Along the diagonal of the diallel matrix are the $n$ $F_1$ inbred parental selves (i.e., a parent strain crossed with itself), and on the off-diagonal are the $(n^2 - n)$ $F_1$ outbred crosses. Those $n^2$ cells of the full diallel matrix consist of replicated observations of trait or fitness values in $F_1$ offspring from each context (in this case, sons and daughters). Hayman\textsuperscript{187} and Lynch and Walsh\textsuperscript{104} emphasize that the original interpretations of this method (given below) assume no environmental and epistatic variance – importantly, the term “environmental” variance here is a quantitative genetic term that is not to be confused with “context” (i.e. niche, sex, environment, etc.), but rather refers to unexplained/residual variance. Grieshop and Arnqvist\textsuperscript{72} approached this by
removing that unwanted noise in the data via a reduced variance-partitioning linear model such that the non-variance-standardized residual observations still consist of additive and dominance variance, but lack environmental and epistatic variance. Note that “environmental” variance pertaining specifically to the focal context should not be removed, for example, Grieshop and Arqvist\textsuperscript{72} did not remove the fixed effect of ‘sex’ or any sex-specific effects. Note also that neither Hayman\textsuperscript{187} nor Lynch and Walsh\textsuperscript{104} necessarily suggest statistically removing these unwanted sources of noise, but rather state their absence as an assumption of the method; hence, Grieshop and Arqvist’s\textsuperscript{72} solution to this is by no means the only one and may not suite other data sets. Still, it is not advisable to directly use raw data for the equations below, as the assumed absence of environmental and epistatic variance are almost certainly violated in any raw data.

The rest of the procedure is based on those residual observations that lack the unwanted noise (see above). Let $\bar{z}_{1,1}, \bar{z}_{2,2}, \bar{z}_{3,3}, \ldots, \bar{z}_{n,n}$ be the vector of means of the F$_1$ parental selves, with subscripts referring to strains 1 through n (Fig S2.1). For all off-diagonal cells of the diallel matrix the subscripted dam is followed by the subscripted sire, for example, a cross between a strain-1 dam and a strain-2 sire would be: $\bar{z}_{1,2}$; and the reciprocal cross: $\bar{z}_{2,1}$ (Fig S2.1). Note that the parental selves are homozygous and that each unique cross is a replicable heterozygote. Also note that the means of reciprocal crosses (e.g., $\bar{z}_{1,2}$ versus $\bar{z}_{2,1}$; Fig S2.1) stem from autosomally identical reciprocal full-siblings that have inherited their sex-chromosomes and cytoplasm from opposite strains. Below we will calculate the “array covariance” (defined below) – a value that describes each strain’s relative degree of dominance over the other strains in the diallel. The array covariances of each strain are calculated for each context (sex) separately, in this case, using separate son and daughter diallel matrices. The example shown below is for the sons of strain-1. Each strain (e.g., strain-1) has a dam- and sire-specific vector of outcrossed means (equations 2.1 and 2.2 below, respectively; Fig S2.1), and the dam- and sire-based array covariances are averaged to attain the array covariance for strain-1. For example, let $r_{\text{dam}}$ be the vector of outbred F$_1$ male (M) means ($\bar{z}$) for the $n-1$ cells in which strain-1 is the dam:
\[ r_{\text{dam}_{M1}}: [\bar{z}_{1,2Mt} \bar{z}_{1,3Mt} \bar{z}_{1,4Mt} \ldots \bar{z}_{1,nMt}] \tag{2.1} \]

\[ r_{\text{sire}_{M1}}: [\bar{z}_{2,1Mt} \bar{z}_{3,1Mt} \bar{z}_{4,1Mt} \ldots \bar{z}_{n,1M}] \tag{2.2} \]

and \( P_{M1} \) be the inbred \( F_1 \) male means of the \( n - 1 \) cells along the diagonal that correspond to the nonrecurrent parental selfs of the strains that \( \text{strain-1} \) was crossed with in order to form those \( r_{\text{dam}_{M1}} \) and \( r_{\text{sire}_{M1}} \) crosses:

\[ P_{M1}: [\bar{z}_{2,2Mt} \bar{z}_{3,3Mt} \bar{z}_{4,4Mt} \ldots \bar{z}_{n,nM}] \tag{2.3} \]

as indicated in Fig S2.1. The average of the two covariances \( COV(r_{\text{dam}_{M1}}, P_{M1}) \) and \( COV(r_{\text{sire}_{M1}}, P_{M1}) \) yields the male-specific array covariance for \( \text{strain-1} \): \( COV_{M1}(r, P) \). Note that averaging \( COV(r_{\text{dam}_{M1}}, P_{M1}) \) and \( COV(r_{\text{sire}_{M1}}, P_{M1}) \) accounts for any parental imprinting that would manifest as differences between reciprocal full-siblings\(^{104} \) (described above), analogous to requiring reciprocal crosses in the allele-specific expression studies (see below). Using the \( F_1 \) female (\( F \)) means (i.e., the daughter diallel matrix) in place of the male means above – which must be estimated independently – would therefore provide the female-specific array covariance for \( \text{strain-1} \): \( COV_{F1}(r, P) \).
Fig S2.1: Diallel cross schematic to aid interpretation of equations (2.1-2.5). Sires 1 through \( n \) (columns) are crossed with dams 1 through \( n \) (rows). After statistically removing unwanted sources of noise (see above), replicate observations of each inbred self or outbred cross are averaged to calculated the means of each cell along the diagonal and off-diagonals, respectively. Shaded cells are those that would be used in equations (2.1-2.3), which would only be sufficient to calculate the array covariance for strain-1 males, \( \text{COV}_{M_1}(r, P) \). Cells with dashed borders correspond to the vector of means in equation (2.1), cells with dotted borders correspond to the vector of means in equation (2.2), and cells with combined dashed/dotted borders correspond to the vector of means in equation (2.3). The covariance between the dashed-border and combined-border cells would be \( \text{COV}(r_{\text{dam}M_1}, P_{M_1}) \), the covariance between the dotted-border and combined-border cells would be \( \text{COV}(r_{\text{sire}M_1}, P_{M_1}) \), and their average would be the array covariance for strain-1 males, \( \text{COV}_{M_1}(r, P) \). That same procedure carried out on the independently observed female data (\( F \), not shown) would be used to calculate the array covariance for strain-1 females, \( \text{COV}_{F_1}(r, P) \). These procedures would be conducted on the relevant cells for calculating the array covariance for the rest of the strains (2 through \( n \)) for males and females separately, so as to produce the vector of male and female array covariances for each strain, \( W_M(r, P) \) and \( W_F(r, P) \), respectively (see equations (2.4) and (2.5)).

The array covariance of each strain relative to one another provides a parametric ordering of strains in terms of whose genetic variation is dominant over whose\(^2\) (Fig S2.2). A relatively high array covariance for a given strain indicates that its genetic variation tends to be recessive to that of the strains it was crossed with in the diallel (Fig S2.2A), as its outbred \( F_1 \) values are a function of who it was crossed to. Conversely, a relatively low array covariance for any strain indicates that its genetic variation tends to be dominant to the strains that it was crossed to (Fig S2.2B), as its outbred \( F_1 \) values are not a function of who it was crossed to. The null expectation is that these underlying allelic effects should be unconditionally
dominant or recessive (i.e., not dominance-reversed), and therefore that the male- and female-specific array covariances among all strains, respectively,

\[ W_M(r, P): [COV_{M1}(r, P), COV_{M2}(r, P), COV_{M3}(r, P) ... COV_{Mn}(r, P)] \] \hspace{1cm} (2.4)

and

\[ W_F(r, P): [COV_{F1}(r, P), COV_{F2}(r, P), COV_{F3}(r, P) ... COV_{Fn}(r, P)], \] \hspace{1cm} (2.5)

should be positively correlated (Fig S2.2C). The same null expectation holds for any set of contexts for which these estimates can be independently derived: the parametric or non-parametric dominance ordination among strains should be positively correlated between contexts. Grieshop and Arnqvist\(^72\) found that both the parametric and non-parametric correlations between \( W_M(r, P) \) and \( W_F(r, P) \) were significantly negative (as in Fig S2.2D), rejecting the null, and indicating that the genetic variation captured within each of their strains tended to be, on average, dominant in one sex but recessive in the other (reviewed above). Ideally, array covariances should be resampled to account for the uncertainty in their estimation, and in turn the uncertainty in the dominance ordination and any correlations of array covariances between contexts.
Fig S2.2: Visual representation of some array covariance and dominance relationships. The simulated data depict scenarios from a diallel cross among 20 strains. Panels (A) and (B) show the 19 points used to estimate the male-specific array covariance for strain-1 via dams, \( \text{COV}(r_{\text{dam}M^1}, P_{M^1}) \) (using equations 2.1 and 2.3), depicting scenarios in which the genetic variation in strain-1 is recessive and dominant, respectively, to that of other strains. When averaged with the same estimate via sires, \( \text{COV}(r_{\text{sire}M^1}, P_{M^1}) \) (using equations 2.2 and 2.3), it would provide the male-specific array covariance for strain-1, \( \text{COV}_{M^1}(r, P) \). This procedure applied to the female data would yield the female-specific array covariance for strain-1, \( \text{COV}_{F^1}(r, P) \). A correlation among strains’ array covariances between males, \( W_M(r, P) \), and females, \( W_F(r, P) \), reveals the extent to which allelic dominance tends to be consistent (C) or reversed (D) between sexes. Regardless, a derived axis (grey line, E) can ordinate strains from those harboring the greatest proportion of male-dominant alleles to those harboring the greatest proportion of female-dominant alleles.
Note that a negative correlation need not be present for this method to still provide utility in identifying a signature of dominance reversal. Consider a scenario wherein the array covariances between contexts are uncorrelated (essentially a circular cloud of points; Fig S2.2E). The cartesian coordinate system may be rotated in order to derive new dimensions \(^5\). A derived axis with a slope of -1 on the original coordinate system would represent a variable describing variation among strains from those with the most dominant alleles in one context to those with the most dominant alleles in the other context (Fig S2.2E), which could have a variety of uses. For example, using that derived axis in a genome-wide association could potentially identify candidate regions in the genome that are associated with dominance reversal between contexts, analogous to Ruzicka et al.'s derived axis of antagonistic additive genetic values. However, note that this would likely be even more underpowered than most GWAS due to the limited number of strains \(n\) that can feasibly be assayed in a diallel cross. For context, Grieshop and Arnqvist\(^7\) conducted 3,278 independent observations of fitness (summed across the sexes) to obtain sex-specific dominance ordination values for only 16 unique genetic lines. Contrast this with Ruzicka et al.'s similarly sized effort, in which 2,230 independent observations of fitness (summed across the sexes) yielded sex-specific additive genetic breeding values for 223 unique genetic lines.

Lastly, regarding the interpretive framework outlined above, note that Hayman\(^1\) derived the analytical theory to show that a regression among strains between the variance in family means, \(V_r\), on the x-axis and the array covariances, \(W_{r,p}\), on the y-axis should result in all strains falling along a single line with slope equal to 1, where the y-intercept indicates the population's average degree of dominance for the underlying loci, and the relative position of strains along that 1:1 line indicates their relative number of dominant/recessive alleles (see Figure 1 in Hayman\(^1\), and Figure 20.4 in Lynch and Walsh\(^1\)). Lynch and Walsh\(^1\) note that measurement error (one source of environmental variance) will cause strains to deviate from this perfect 1:1 line, but that the regression coefficient should not be significantly different from one unless the inbred parental strains actually feature substantial heterozygosity or there is significant epistatic variance. However, as Grieshop and Arnqvist\(^7\) point out, the fact that the y-intercept should
indicate the average dominance coefficient of the underlying loci, and that strains should be fixed for various combinations of alleles across the genome, assumes that the dominance coefficients of alternative alleles are not conditional in any way upon the context in which they were measured, which seems unlikely, especially in light of the evidence reviewed in the main text. Indeed, Grieshop and Arnqvist’s\(^2\) inbred strains did not fall on a 1:1 line upon regressing \(V_r\) and \(W_{r,p}\) in either males or in females, despite having removed environmental and epistatic variance, indicating that their strains exhibited varying average degrees of dominance due to being fixed for different combinations of alleles. Thus, Grieshop and Arnqvist\(^2\) focused on comparing the array covariances between contexts (males and females); after all, if the relative position of strains along the 1:1 line should indicate their relative number of recessive alleles then so should their relative position along either the x- or y-axis alone, the latter of which carries the intuitive logic outlined above and in Fig S2.2. That said, it is possible that strains’ relative values along the 1:1 line between \(V_r\) and \(W_{r,p}\) , rather than along the latter axis alone, prove useful for some data sets.

**Allele-specific expression**

Reversed patterns allele-specific expression between different life stages, traits, tissues, sexes or environments is a promising method to screen for dominance-reversed loci. As a proof of this concept, we have shown (Box 2, S1) that competition between alternative transcription factor alleles for binding a downstream transcription factor binding site is sufficient to generate adaptive reversals of dominance that stabilize antagonistic polymorphisms, and that this results in an imbalance in the expression level of that polymorphism’s alternative alleles that is reversed between contexts.

There are broadly two alternative allele-specific expression designs that are capable of revealing this pattern empirically: the “F\(_1\) hybrids” approach and “common reference” approach\(^{144}\). The F\(_1\) hybrids design crosses two inbred/homozygous strains and maps each RNA-Seq read from F\(_1\) hybrid offspring back to both parental genomes\(^{144,199}\). Differential mapping efficacy of short RNAseq reads to one or the other parental genome indicates to which allele (paternal or maternal) each read belongs. Differences in read
mapping coverage between alternative alleles expressed by F\textsubscript{1} hybrids indicates allelic imbalance in expression\textsuperscript{144,199}. Opposite patterns of allelic imbalance between contexts would represent candidate dominance reversed genes. Alternatively, the common reference design works by crossing a panel of focal inbred strains to a common tester strain and therefore creating a panel of hybrid families that share half of their genomes\textsuperscript{144,200}. Within-family allelic imbalance between the focal and tester alleles that are reversed between contexts would likewise indicate candidate dominance reversed genes. In either design, assigning reads can be facilitated by long-read technologies such as Iso-Seq\textsuperscript{192,201,202} or linked-read sequencing applied to transcriptomic data\textsuperscript{203} – note, however, that sufficient coverage is important for quantifying the magnitude and direction of allelic imbalance.

Under both experimental designs, reciprocal crosses are needed in order to rule out parental imprinting effects (analogous to the use of reciprocal crosses in dominance ordination, above), and allelic imbalance can only be concluded after accounting for intrinsic allele-specific mapping bias\textsuperscript{144}. The latter is typically assessed by mapping F\textsubscript{1} hybrid genomic reads (for which alternative autosomal alleles are exactly equally abundant) back to each parental genome and either excluding those sites for which there is differential genomic-read mapping efficacy, or correcting for its direction and magnitude at each site. Further still, opposite patterns of allelic imbalance between contexts should really only be considered as true-positives if the magnitude of allelic imbalance is significant in both contexts independently, since statistically significant allele-by-context interactions could include sites that exhibit allelic imbalance in one context but not the other (i.e., sites that are not reversed). Lastly, allelic imbalance between alternative contexts would ideally be assessed in multiple genetic backgrounds to account for confounding background genetic effects. This is partly inherently achieved by the common reference approach, but the F\textsubscript{1} hybrids approach would require independent crosses of unique inbred strains to be analyzed in parallel and only those dominance-reversed genes that are consistent among different genetic backgrounds would represent true-positive cases of dominance reversal.
Still, interpreting gene expression data in the context of dominance reversal is not straightforward and caution must be taken seriously. Namely, the connection between a reversed pattern of allelic imbalance and selection or fitness will typically be lacking. Strictly speaking, if the aim is to utilize these patterns of reversed allelic imbalance to assist the identification of candidate loci under antagonistic pleiotropy then this would ultimately require confirmation of genotypic fitness effects and/or genomic signatures of balancing selection that lend an independent line confirmation (but see Additional considerations in the main text regarding genomic patterns of balancing selection).

Allele-specific expression studies also enable the decomposition of variation into cis-, trans- and cis-by-trans effects via comparisons between parents and F1s as well as among F1 families, depending on the design144. As pointed out in the Chen et al.159 example (main text), this kind of empirical data can enhance our understanding of the proximate genetic mechanisms that may effectively represent a “dominance modifier” that could enable beneficial reversal of dominance93, and biophysically explicit models of the gene regulation (Box 2) can facilitate the interpretation of empirical patterns.