Intralocus Sexual Conflict

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Intralocus sexual conflict arises when there are sex-specific optima for a trait that is expressed in both sexes and when the constraint of a shared gene pool prevents males and females from reaching their optima independently. This situation may result in a negative intersexual correlation for fitness. Here I first discuss key differences between intra- and interlocus conflict, the type of sexual conflict that arises in mating interactions between males and females. I then review the experimental evidence for the existence of genomewide sexually antagonistic variation and discuss how intralocus conflict can be resolved. Substantial genomewide sexually antagonistic variation exists in *Drosophila melanogaster* lab populations. Yet, in the same species, sex-specific gene regulation appears to evolve rapidly, suggesting that the obstacles to the resolution of intralocus conflict are minor. The fact that negative intersexual correlations for fitness are observed even if sexual dimorphism can evolve rapidly suggests that intralocus conflict is highly dynamic. The final part of this review examines the evolutionary consequences of intralocus sexual conflict for the evolution of the sex chromosomes, sexual selection, and sex determination. Intralocus conflict helps to explain many of the peculiar features of the sex chromosomes and has shaped the functional bias and expression biases of sex-linked genes. The genomic distribution of sexually selected genes, in particular, affects sexual selection in various ways. The presence of sexually antagonistic variation can strongly interfere with the good genes' process of sexual selection and erode the genetic benefits of mate choice. Regarding sex determination, this review concentrates on evolutionary transitions between different sex determination mechanisms. Such transitions have occurred frequently in several taxa. Theory and empirical data suggest an important role for intralocus conflict in triggering switches between sex determination systems.

Key words: **sexual conflict; sexual dimorphism; sexually antagonistic selection; sex chromosomes; sex determination**

Introduction

A female and a male engaging in sexual reproduction have a shared interest in the production of offspring, but they typically disagree on many organizational aspects of their reproductive interaction (Trivers 1972; Parker 1979; Partridge & Hurst 1998; Arnqvist & Rowe 2005; Chapman 2006). Differences between the sex roles set the stage for an evolutionary conflict of interests between males and females. This conflict may manifest itself in two ways: individuals in one sex can evolve traits that enhance their own reproductive success at the cost of the fitness of their mating partners (interlocus sexual conflict (Chapman et al. 2003), or males and females can come in conflict over the contents of their shared gene pool when the two sexes are subject to opposing selection pressures (intralocus sexual conflict; Rice & Chippindale 2001).

Manifestations of Sexual Conflict

Interlocus conflict, that is, conflict over the outcome of intersexual interactions, explains

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such strategies as sexual coercion (Clutton-Brock & Parker 1995), mate guarding, and other tactics to prevent the partner from remating (e.g., Watson et al. 1998), physical or physiological harassment of the partner aimed at reducing the success of competitors (e.g., Chapman et al. 1995), evasion of parental care (e.g., Trivers 1972; Royle et al. 2002), and resistance against mating (Holland & Rice 1998). The term *interlocus conflict* refers to the fact that sexually antagonistic adaptation in one sex may induce counteradaptation in the other sex. For example, to reduce the harmful consequences of male accessory gland proteins, females may reduce their remating rate or evolve physiological counteradaptations of their reproductive tract (Chapman et al. 1995; Arnqvist & Rowe 2005). In this way, the interaction between male and female mating traits, genetically encoded by independent sets of genes, can potentially lead to continued sexually antagonistic coevolution of mating strategies (Rice & Holland 1997; Holland & Rice 1998; Rice 1998a; Chapman et al. 2003).

Intralocus sexual conflict, by contrast, involves a single phenotypic trait that is encoded by the same set of genes in females and males. A potential for this type of sexual conflict arises when there are different optima for a trait that is expressed in both sexes. The functional divergence of gender roles leads to sex-specific optima for many traits that are expressed in the context of sexual selection and reproduction (Parker 1979). The combined action of sexual selection on one sex and opposing natural selection acting on the two sexes together commonly gives rise to a regime of sexually antagonistic selection on such traits. For example, opposing selection between the sexes has been demonstrated for bill color in zebra finches (*Taeniopygia guttata*), a costly male sexual ornament that is expressed in both sexes (Price & Burley 1994); for horn phenotype in Soay sheep (*Ovis aries*) (Robinson et al. 2006); and tail length in the serin (*Serinus serinus*) (Björklund & Senar 2001). Specific variants of the last two traits increase success in male–male competition but are costly to produce for females.

The causal connection between sex role differences and sexually antagonistic selection is not always as clear as for traits that function in mate choice or mate competition. Also, traits that are not directly involved in sexual selection may be selected antagonistically across the sexes. Collared flycatchers (*Ficedula albicollis*), for example, are subject to sexually antagonistic selection on body size (Merilä et al. 1997). Presumably, this is a result of sex-specific differences in the timing of migration and an associated exposure of males to stressful conditions in early spring that favor a smaller body size in males. In the European adder (*Vipera berus*), the optimal color pattern is different for males and females because of the difference between the sexes in the relative importance of thermoregulation versus camouflage (Forsman 1995).

Differences between Inter- and Intralocus Conflict

The distinction between inter- and intralocus sexual conflict is useful for two reasons. First, the two types of conflicts are played out at very different levels of biological organization that offer different means and scope for conflict resolution. Intralocus conflict revolves around constraints set by the developmental system that prevent the sexes from reaching their evolutionary optima independently (Lande 1980). Resolution of intralocus conflict can therefore be achieved by genetic mechanisms that decouple developmental pathways in males and females, such as sex linkage and sex-specific gene regulation (Badyaev 2002; Chenoweth et al. 2008). By contrast, the battleground for interlocus conflict lies at the level of reproductive interactions between individuals. The feasibility of manipulation, its costs and benefits, and the costs and benefits of resistance constrain the strategic options for males and females. Accordingly, the biological context (e.g., mating system, life history, and ecological conditions)

sets the scope for interlocus sexual conflict and the potential for its resolution (Lessels 2006).

A second reason to distinguish inter- and intralocus conflict is that the two types of sexual conflict have different evolutionary consequences. Apart from its direct and obvious consequences for the evolution of mating strategies and sexual selection (Arnqvist & Rowe 2005), interlocus conflict has been proposed as a catalyst for accelerated evolution because of its tendency to generate coevolutionary arms races (Rice & Holland 1997; Holland & Rice 1998). One would expect such arms races to result in the rapid evolution of reproductive traits (Gavrilets et al. 2001), potentially leading to reproductive divergence between populations and, ultimately, speciation (Parker & Partridge 1998; Rice 1998a; Gavrilets 2000; Arnqvist & Rowe 2005). The biological relevance of sexually antagonistic arms races is currently debated (e.g., Long et al. 2006; Bacigalupe et al. 2007; McPeek et al. 2008), and several authors have argued that coevolutionary arms races resulting in harmful behavior are by no means the only possible outcome of interlocus conflict (Rowe et al. 2005; Lessels 2006).

Intralocus conflict has also been hypothesized to contribute to speciation, but by a different mechanism: sexual dimorphism or sex limitation that evolved separately in different populations in response to sexually antagonistic selection could break down in hybrids, resulting in decreased survival of hybrid offspring and partial postzygotic isolation (Parker & Partridge 1998; Rice & Chippindale 2002; Michalak & Noor 2003). More important, intralocus sexual conflict has consequences for the evolution of the sex chromosomes (Bull 1983; Rice 1987; Charlesworth 1991), sex determination (Rice 1986; Kraak & Pen 2002; Van Doorn & Kirkpatrick 2007), genomic imprinting (Day & Bonduriansky 2004; Patten & Haig 2008), and gene regulation (Ellegren & Parsch 2007). The existence of genomewide sexually antagonistic variation in fitness (Chippindale et al. 2001; Prasad et al. 2007; Foerster et al. 2007) carries implications for sexual selection (Brommer et al. 2007; Pischedda & Chippindale 2006), sex ratio allocation (Alonzo & Sinervo 2007), and aging (Vieira et al. 2000; Bonduriansky et al. 2008).

Sexual conflict has recently been reviewed elsewhere (Chapman et al. 2003; Arnqvist & Rowe 2005; Chapman 2006; Lessels 2006), but intralocus conflict has received limited attention in these reviews. Nevertheless, since the groundbreaking experimental work (Rice 1992), much progress has been made in understanding the evolutionary ramifications of intralocus sexual conflict. The aim of this report is to bring together these new insights from different lines of research ranging from molecular genetics to field ecology. To structure the review, I will first focus on sexually antagonistic variation *per se*, discuss the evidence for its existence, and address the issue of conflict resolution. Next, I will review the evolutionary implications of intralocus conflict.

Why Do We Observe Sexually Antagonistic Variation in Fitness?

Evolutionary biology has a well-established theory of selection (e.g., Fisher 1958) but is still in the process of formulating a theory of the constraints on evolution (Brakefield 2006). This may well explain why it is difficult to assess the evolutionary significance of intralocus sexual conflict; different standpoints on the role of constraints on adaptation can strongly color expectations on the evolutionary significance of intralocus conflict. One could argue that intralocus conflict must have a profound effect on adaptation because the gender roles are so fundamentally different that one would expect different optima for virtually every phenotypic trait. This argument implicitly assumes that males and females cannot easily adapt to sex-specific optima. Yet, the constraint of a shared gene pool between the sexes can easily be evaded by the evolution of sexual dimorphism. One could therefore just as easily dismiss intralocus conflict as a transient phenomenon without much of an effect on

long-term evolution, arguing that intralocus conflict would always quickly be resolved. The two opposite positions are difficult to reconcile. Both are to some extent supported by data, which the field has been struggling to integrate (Arnqvist & Rowe 2005). Before presenting the unifying perspective that is emerging from the ongoing debate, I will first review the empirical evidence for the widespread occurrence of sexually antagonistic variation and then discuss the relevance of constraints on sex-specific adaptation on the basis of what is currently known about the evolution of sexual dimorphism.

Empirical Evidence for Genomewide Sexually Antagonistic Variation

Evidence for the existence of sexually antagonistic genetic variation comes from studies that demonstrate sexually antagonistic selection on a phenotypic trait, segregating genetic variation subject to such selection and the absence of perfect sex-specific expression, which combine to generate a genotype × sex interaction for fitness. Studies of this kind have been carried out in several animal (e.g., Forsman 1995; Merilä et al. 1997 and Merilä et al. 1998; Robinson et al. 2006; Foerster et al. 2007; Brommer et al. 2007) and dioecious plant (e.g., Kohorn 1994; Delph et al. 2004) species, but ideally one would like to see a substantially longer list of examples (see Cox & Calsbeek 2009 for a review of current data). The difficulties of unraveling the genetic basis of phenotypic variation along with estimating its sex-specific fitness consequences have obstructed the documentation of sexually antagonistic variation across a wide range of species. In fact, the most detailed and convincing evidence for the occurrence of genomewide sexually antagonistic variation comes from a series of experiments by W.R. Rice et al. on laboratory stocks of *Drosophila melanogaster*, a species for which unique genetic tools and experimental protocols are available (Rice & Chippindale 2001).

In the first experiment (Rice 1992), a population that was variable for eye color alleles at two autosomal loci was allowed to propagate for 29 generations. Each new generation of offspring contained males and females with all possible combinations of eye color alleles, but the experimental protocol allowed only females with a specific combination of alleles to reproduce; males with that same combination of alleles were removed from the population before reproduction. As a result of this manipulation, the combination of autosomal eye color alleles segregated as if it were a female-determining allele at a novel sex determination locus. At nearby loci that segregate for sexually antagonistic alleles, one would expect positive linkage disequilibrium to develop between alleles that are beneficial to females but detrimental to males and the female-determining alleles at the eye color loci (Rice 1984). Indeed, when the artificial female-determining markers were expressed in males at the end of the experiment, the fitness of these males was markedly reduced, but a concordant increase of female fitness could not be statistically demonstrated (Rice & Chippindale 2001). Genetic drift was unlikely to have caused the decline in male fitness, and reduced male fitness was not observed in control populations. This finding led Rice (1992) to conclude that female-benefit/male-detriment sexually antagonistic variation had accumulated in regions that were near the artificial female-determining genes.

In a second experiment (Rice 1998b), specially constructed clone-generator lines were used to consistently express a nearly complete haploid genome in males for 41 generations, as if it were a giant nonrecombining Y chromosome. Again, accumulation of sexually antagonistic variation could most clearly be demonstrated based on the observed changes in male fitness. Experimental males scored better than control males on a variety of fitness measures. Expression of the synthetic Y chromosome in females resulted in retarded development, but no other adverse female fitness effects were found.

Demonstrating a fitness reduction from the expression of masculinized genomes in females constitutes critical evidence for the existence of sexually antagonistic variation and its maintenance by sexually antagonistic selection. The lack of a clear reduction in female fitness in Rice's second experiment (Rice 1998b) leaves room for an alternative interpretation of the results. Because females were taken every generation anew from an independent stock, they could not evolve counteradaptations to novel male reproductive strategies. Therefore, males had an inherent advantage in interlocus sexual conflict (cf. Rice 1996). Even though all male fitness assays were performed with tester females from an independent stock, the female partners of experimental males did suffer a higher mortality and sterility than females that were mated to control males. This finding suggests that an advantage in interlocus conflict was at least partially responsible for male fitness gain (Rice 1998b).

In an attempt to disentangle the effects of intra- and interlocus conflict, Prasad et al. (2007) recently replicated Rice's experiment with larger selection experiments and more extensive assays of female fitness to improve statistical power. The experimental protocol was slightly modified to facilitate the detection of recessive X-linked effects—theory predicts such effects to be prevalent (Rice 1984). The recent experiment confirmed the earlier observations. After 25 generations of male-limited evolution, sexually dimorphic traits had evolved in the direction of the male optimum, leading to an increase in male fitness. More important, Prasad et al. (2007) also observed a concordant decrease in female fitness when the male-limited genomes were expressed in females.

The previously discussed studies (Rice 1992, 1998b; Prasad et al. 2007) examine the accumulation of sexually antagonistic variation over the course of several generations when expression of a portion of the genome is limited to one sex. A complementary perspective on intralocus conflict is offered by a snapshot of the pattern of sexually antagonistic variation that is present in a population at a single point in time. Chippindale et al. (2001) obtained such a snapshot by cytogenetically cloning 40 genomic haplotypes randomly selected from a lab stock at a single point in time. The genomic haplotypes were expressed in many genetic backgrounds in both males and females, and their fitness in these backgrounds was measured. Doing so provided data from which the genetic covariance for fitness between the sexes could be estimated. Juvenile fitness correlated positively between the sexes, but a negative correlation was found for adult fitness, where gender roles are most divergent. There was also a strong intersexual interaction for total fitness: genomes that performed well in males were associated with low fitness when expressed in females, and vice versa.

Collectively, these experiments suggest that a substantial fraction of standing fitness variation in *Drosophila* lab populations is attributable to unresolved intralocus conflict. What about wild populations? The relevance of studies on *Drosophila* lab populations to understanding evolution in the wild has been debated in various contexts (e.g., Mallet 2006). The rather constant environment of the lab may induce a substantial reduction in adult fitness variation relative to that in wild populations. One would therefore expect lab studies to overestimate the contribution to fitness variation by sexually antagonistic alleles (Chapman et al. 2003). In fact, variation that is concordantly selected in males and females builds a positive intersexual genetic correlation for fitness that could even outweigh the negative intersexual genetic correlation expected under intralocus conflict.

Data from another *Drosophila* lab study suggest that these concerns could well be valid. Rather than expressing a certain fraction of the genome consistently in one sex, Morrow et al. (2008) relaxed selection in one sex while maintaining selection in the other. After 26 generations of such asymmetrical selection, the fitness of the unselected sex had dropped relative to the fitness in the selected sex, consistent with the accumulation of sexually antagonistic

alleles. However, relative to the base population, the fitness of both sexes had decreased. A likely explanation for this result is that the relaxation of selection in one sex had nearly doubled the genome-wide mutational load, leading to a substantial reduction in fitness in both sexes (Morrow et al. 2008). Given that natural populations show higher environmental variance for fitness and are likely to exhibit a higher load of (conditionally) deleterious mutations than lab populations, it would indeed be no surprise to find high and positive intersexual correlations for fitness in the wild.

Contrary to this expectation, two recent field studies, both based on long-term population data, report negative intersexual correlations for lifetime fitness. Individual life history data on a population of red deer (*Cervus elaphus*) collected over 34 years revealed a significant negative correlation between the fitness estimates for related males and females (Foerster et al. 2007). Similar information collected for a population of collared flycatchers (Brommer et al. 2007) yielded a negative point estimate (significantly different from +1, but not from 0) for the genetic correlation between male and female lifetime reproductive success. Because of the difficulty of measuring sexually antagonistic variation directly in natural populations, both of these studies extracted fitness estimates and genetic parameters from pedigree information, using animal model analysis (Kruuk 2004).

Clearly, more studies on natural populations are needed to assess the overall significance of intralocus conflict in the wild. However, because other sources of fitness variation would tend to conceal the signature of sexually antagonistic variation, observations of significant negative intersexual correlations for fitness in the wild seem to me indicative of the evolutionary relevance of intralocus sexual conflict.

The Resolution of Intralocus Conflict

Intralocus sexual conflict can be mitigated through the independent evolution of the sexes toward their sex-specific optima, resulting in sexual dimorphism (Fisher 1958; Lande 1980). From the observations that genomewide sexually antagonistic variation is prevalent, one would naively expect this process to be severely constrained, but the evolution of sexual dimorphism is a biologically widespread phenomenon (Badyaev 2002).

There has been a longstanding interest in the genetic mechanisms that allow for phenotypic divergence between the sexes. Quantitative genetics theory predicts that independent evolution of the two sexes is constrained by the intersexual genetic correlation r_{MF} (Lande 1980; Cheverud et al. 1985). This quantity measures to what extent selection on a character in one sex generates a correlated response in that same character in the other sex. A positive intersexual genetic correlation for a phenotypic trait that is subject to sexually antagonistic selection would give rise to a negative genetic correlation for fitness for that trait (Fig. 1). As long as genetic variance for sex-biased expression is present, the intersexual genetic correlation will be less than perfect, which allows males and females to evolve in the direction of their sex-specific optima (Fisher 1958; Lande 1980). However, this process can be very slow if r_{MF} is close to unity.

Empirical measurements of r_{MF} indicate that the intersexual genetic correlation for phenotypic traits is often large (e.g., Lande 1980; Meagher 1992; Roff 1997; Merilä et al. 1998; Delph et al. 2004; Mank 2007; Chenoweth et al. 2008) and that r_{MF} correlates negatively with sexual dimorphism across traits (Bonduriansky & Rowe 2005). It is not exactly clear how these results should be interpreted, however. Comparisons of intersexual genetic correlations across traits provide estimates of the relative importance of constraints, but it is problematic to interpret r_{MF} as an absolute measure of constraint on sex-specific adaptation: given enough time to accumulate sex-biased mutations, even genetic systems characterized by a high value of r_{MF} can achieve perfect sex-specific adaptation. Furthermore, several authors have argued that

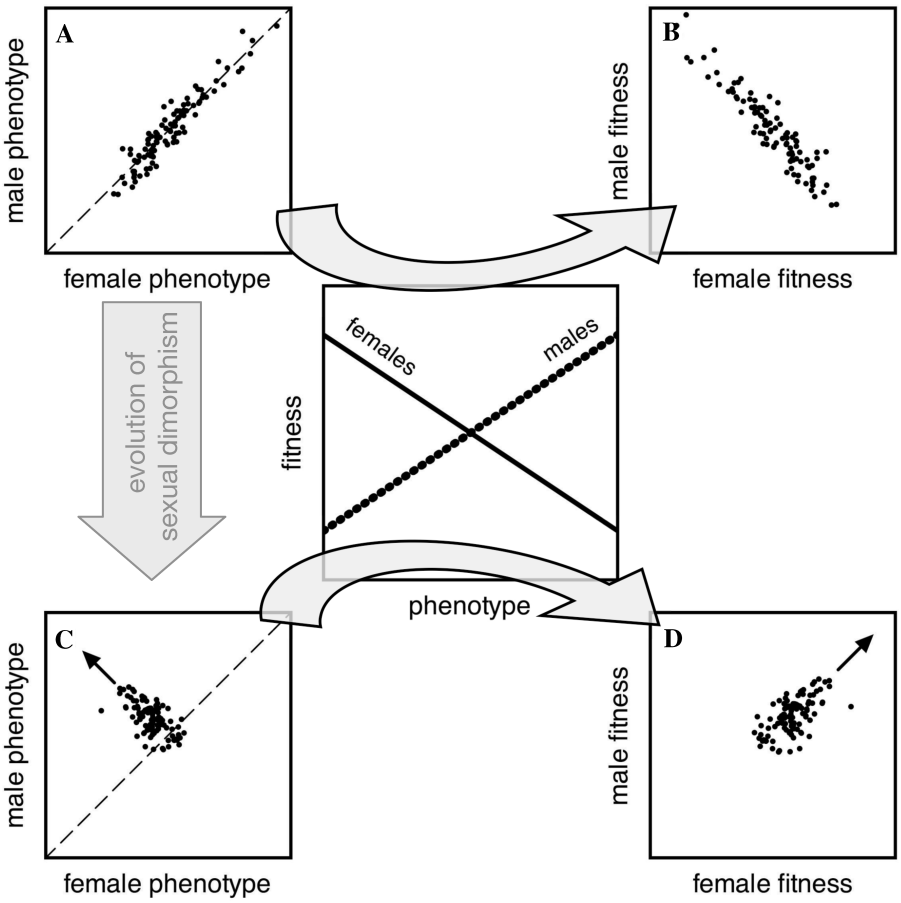

Figure 1. Resolution of intralocus conflict by the evolution of sexual dimorphism. Phenotypic traits that are expressed in both sexes typically show a high intersexual genetic correlation. (**A**) This panel shows how male and female phenotypes are related for a hypothetical population distribution of genotypes. Each dot represents a single genotype. The points cluster around the diagonal (dashed line), indicating that the intersexual genetic correlation is close to 1. If the phenotypic trait is subject to sexually antagonistic selection (central panel) then the genotypes that perform well in males are associated with a low fitness in females and vice versa. The genotype distribution in panel A thus gives rise to a negative intersexual correlation for fitness (**B**). The evolution of sex-specific gene regulation allows the phenotype distribution to move away from the diagonal (**C**) and can strongly reduce the intersexual genetic correlation. This allows males and females to each independently move towards their phenotypic optima (**D**), such that the sexual conflict is eventually resolved.

the underlying genetic architecture of sexual dimorphism is not adequately represented by quantitative genetic parameters such as r_{MF} (Reeve & Fairbairn 1996; Rhen 2000; Badyaev 2002). The quantitative genetic model poorly predicts the outcome of artificial selection experiments (Reeve & Fairbairn 1996), and it is inconsistent with empirical examples of rapid changes in sexual dimorphism in response to the environment (reviewed in Badyaev 2002).

A plausible explanation for the discrepancy is that the genetic architecture of sexual dimorphism can respond quickly to sexually antagonistic selection by adjusting sex-specific gene regulation or evolving other mechanisms of sex-specific epistasis. Such processes are likely to affect sex-specific genetic variances and

heritabilities. Little is known about how rapidly and how strongly these parameters change in the course of sex-specific adaptation. The evolution and stability of the G matrix, which summarizes the pattern of segregating genetic variation, has not been investigated for genetic systems that include epistasis and sex-specific selection (Hansen 2006; Arnold et al. 2008). Yet, unanticipated patterns of sex-specific heritabilities and genetic variances have been observed in simulations and empirical studies that examine the evolution of sexual dimorphism (Rhen 2000; Reeve & Fairbairn 2001; Bonduriansky & Rowe 2005). Hence, it is unlikely that the existing quantitative genetic model, with its simplifying assumptions of additive gene effects, a constant genetic architecture, and equal and constant heritabilities for males and females (Lande 1980, Cheverud et al. 1985), will be able to quantitatively capture the evolutionary dynamic of sexual dimorphism. In view of these considerations, instantaneous measurements of r_{MF} are probably more informative about past selection patterns than about current and future constraints on the evolution of sexual dimorphism.

At the genetic level, changes in the genetic architecture of sexual dimorphism can be brought about by a variety of mechanisms (Chenoweth et al. 2008). Some of these, such as the translocation of genes to the sex chromosomes (Charlesworth & Charlesworth, 1980; Rice 1984; Bachtrog 2006), gene duplication followed by the evolution of sex-limited expression (Baur et al. 2008), or the evolution of parent-of-origin effects through genomic imprinting (Day & Bonduriansky 2004; Patten & Haig 2008), are likely to occur on a long time scale, whereas others, such as the evolution of sex-specific gene regulation, may occur more rapidly (Ellegren & Parsch 2007). Indeed, comparative analyses of genomewide gene expression profiles show for a variety of organisms that a substantial proportion of the genes exhibits sex-biased expression (Parisi et al. 2004; Connallon & Knowles 2005; Rinn & Snyder 2005; Gnad & Parsch 2006) and that patterns of sex-biased gene expression are labile (Ranz et al. 2003; Pröschel et al. 2006; Ellegren & Parsch 2007). For example, in both *Drosophila melanogaster* and *Drosophila simulans* about half of the genes show sex-biased expression. Among the 3,349 genes with sex-biased expression in at least one of the species, 951 genes (28%) have gained, lost, or reversed sex-biased expression since the divergence of *D. melanogaster* and *D. simulans* ~2.5 million years ago, and another 952 genes show an increase or decrease in sex-biased expression when compared between *D. melanogaster* and *D. simulans* (Ranz et al. 2003). Differences in sex-biased gene expression thus account for most (>80%) gene expression differences between the two species; 2,283 genes exhibit differential expression between *D. melanogaster* and *D. simulans*, which amounts to slightly less than half of the genes (Ranz et al. 2003).

A closer inspection reveals that male-biased genes are overrepresented among those that show variation in expression levels (Meiklejohn et al. 2003; Ellegren & Parsch 2007). What evolutionary forces drive the rapid divergence of predominantly male-biased genes is not exactly clear, but various molecular signatures (e.g., the ratio of nonsynonymous over synonymous substitutions, reduced codon bias, and gene duplication rates) suggest that male-biased genes are exposed to positive selection (Swanson & Vacquier 2002; Meiklejohn et al. 2003; Pröschel et al. 2006). The finding that males experience stronger sexually antagonistic selection than females is consistent with the observation that fitness effects of intralocus conflict could more easily be demonstrated for males than for females in *D. melanogaster* population-genetic experiments (Rice 1992; Rice 1998b; Prasad et al. 2007).

A Unifying Dynamic Perspective

Regulatory variation is abundantly available in natural populations (e.g., Rockman & Wray 2002), and the comparative analyses discussed previously show that patterns of sex-specific

epistasis can change rapidly through the evolution of sex-biased modifiers to the expression of sexually antagonistic loci. Moreover, the evolution of sex-specific gene regulation is just one of several mechanisms by which genetic constraints between the sexes can be overcome (Chenoweth et al. 2008). Taken together, this would seem to indicate that the obstacles to the resolution of intralocus conflict are minor. Why then do we observe so much sexually antagonistic variation, and even negative genetic intersexual correlations for fitness?

At the moment the answers to this question are speculative. Perhaps the resolution of intralocus conflict can be easily achieved for some genes but not for others. Specifically, it may be difficult to evolve toward sex-specific optima for genes with multiple functions in multiple tissues because such genes experience significant constraints on adaptability (Ellegren & Parsch 2007). Indeed, a recent analysis of mouse and chicken microarray data shows that sex-biased genes are expressed in a smaller range of tissues than unbiased genes (Mank et al. 2008). This pattern is expected if pleiotropic constraints hamper the resolution of sexual conflict but also if tissue-specific genes are more common among sexually antagonistic genes than among genes that are concordantly selected in both sexes. A comparative analysis of gonad-specific genes versus tissue-specific genes that are less obviously involved in the divergence of the sex roles could give a first indication which of these alternatives explains the relationship between pleiotropic constraints and sex-biased gene expression.

A second explanation that could reconcile the occurrence of sexually antagonistic variation with the observation that conflict resolution can evolve rapidly is that intralocus conflict itself is highly dynamic. Standing sexually antagonistic variation may simply result from transient polymorphisms for sexually antagonistic alleles across many loci (Rice & Chippindale 2001). Many genes exhibit sex-biased expression patterns to start with, and it seems likely that mutations in those genes would also have sex-specific effects. Accordingly, the influx of new sexually antagonistic alleles by mutation could be considerable. On top of that comes the lability of sexual selection, which may induce inherently variable sexually antagonistic selection pressures (Rice & Holland 1997; Wiens 2001; Ranz et al. 2003). Finally, extensive epistatic interactions between sex-biased genes and sexually antagonistic genes (Chippindale & Rice 2001) contribute to the dynamic nature of intralocus conflict. Evolutionary change in the former will modify the selection pressures acting on the latter and potentially trigger continual coevolution between sexually antagonistic loci and sex-limited loci (Rice & Chippindale 2002). The joint action of these factors may cause sexual antagonism to change on a time scale that is fast relative to the rate at which conflict can be resolved. If this is indeed the case, one would expect sex-biased expression to evolve for genes that are consistently under sexually antagonistic selection, only partial resolution of the conflict for genes that experience more labile selection regimes, and a considerable remaining gender load caused by sexually antagonistic alleles.

Evolutionary Implications of Intralocus Sexual Conflict

The existence of sexually antagonistic variation has consequences for genome organization, sexual selection, aging, sex ratio allocation, and several other topics that are central to the interests of evolutionary biologists. In what follows I will concentrate on three topics that have most extensively been associated in the literature with sexual antagonism: the evolution of the sex chromosomes, mate choice, and sex determination. I will not review the smaller literature on the evolution of genomic imprinting as a consequence of intralocus conflict. Instead, I refer to Day and Bonduriansky (2004) and Patten and Haig (2008) for a discussion on that interesting topic.

Sexual Conflict and the Sex Chromosomes

Sexual conflict figures prominently in the established theory for the origin of sex chromosomes (Bull 1983; Rice 1987; Charlesworth 1991; Charlesworth & Charlesworth 2005). Strongly differentiated sex chromosomes have evolved independently in different lineages and show several common features (Bull 1983). Recombination is suppressed in the heterogametic sex, and the Y (in species with male heterogamety) or W (in species with female heterogamety) chromosome has often genetically degenerated. Lack of recombination between the sex chromosomes may initially evolve to avoid the production of disadvantageous intersexual phenotypes (Charlesworth & Charlesworth 1978), and primitive sex chromosomes often feature small nonrecombining regions that presumably contain the sex-determining genes (Westergaard 1958; Bull 1983). However, sexually antagonistic genes are thought to be responsible for the wider spread of nonrecombining regions along much of the length of the sex chromosomes. Linkage to a sex-determining locus favors the accumulation of sexually antagonistic alleles that are favorable to the heterogametic sex (Fisher 1958; Charlesworth & Charlesworth 1980), and selection subsequently favors the evolution of reduced recombination between the sex-determining gene and the sexually antagonistic loci in its vicinity (Bull 1983; Rice 1987). As recombination is progressively suppressed over larger and larger regions, the sex chromosomes can accumulate additional sexually antagonistic variation, leading to increased functional specialization and providing additional selection pressure to reduce genetic exchange between the sex chromosomes.

Nonrecombining regions of the Y and W chromosomes tend to accumulate deleterious alleles, eventually leading to a nearly complete degeneration of these chromosomes (Charlesworth 1991). The loss of genes from the Y and W chromosomes is often compensated for by dosage compensation, that is, regulatory mechanisms that ensure equal gene expression of X- or Z-linked genes in the homo- and heterogametic sex (Charlesworth 1978; Charlesworth 1996). The evolution of dosage compensation provides one more example of sexual conflict (Engelstädter & Haig 2008). Because of the different copy numbers of X- or Z-linked genes in males and females, the sexes are in conflict over the expression level of these genes whenever the optimal dosage of gene products is similar for males and females. The conflict can be resolved in various ways (Charlesworth 1996). In mammals, for example, dosage compensation is achieved by random inactivation of one of the X chromosomes in females. A parallel mechanism of random Z chromosome inactivation is not found in birds (Ellegren 2002). It has been suggested that X inactivation in the soma of females derives from X inactivation in the germ line during spermatogenesis (Lyon 1974; Charlesworth 1978): it appears that Z inactivation during oogenesis, which could have served as the evolutionary precursor of random Z inactivation in birds, has not evolved (Kaiser & Ellegren 2006).

Interestingly, the evolution of X inactivation in the germ line has been explained as yet another consequence of sexual conflict. Wu and Xu (2003) propose that the duplication onto the autosomes of X-linked, sexually antagonistic genes that act during late spermatogenesis (Betrán et al. 2002) sets the stage for a functional differentiation of the X chromosome. As the autosomal gene specializes on its function in spermatogenesis, the X-linked gene can favor female functions. The late stage of spermatogenesis thus becomes less and less dependent on the X chromosome, and it becomes advantageous to inactivate the X chromosome during spermatogenesis to silence X-linked female-benefit/male-detriment alleles that could interfere with spermatogenesis. The hypothesis generates several testable predictions, but so far its validity could be evaluated based on only limited data (Wu & Xu 2003).

The selective regimes for sexually antagonistic alleles differ widely between the two sex chromosomes (Fisher 1958; Rice 1984). In species with XY/XX sex determination, the nonrecombining region of the Y chromosome follows strict patrilineal inheritance, such that Y-linked genes are selected only in males. As a consequence, male-benefit/female-detriment alleles can accumulate on the Y chromosome irrespective of the magnitude of the deleterious effect in females. An X chromosome, on the other hand, spends two-thirds of its time in females and only one-third of its time in males. Dominant female-benefit/male-detriment alleles can therefore more easily be maintained on an X chromosome than on an autosome. Moreover, because the X chromosome is hemizygous in males, recessive X-linked male-benefit alleles are immediately exposed to selection in males, and such alleles are more likely to invade on an X chromosome than on an autosome. Consistent with these theoretical predictions is the finding that the sex chromosomes contribute disproportionately to sexually antagonistic variation. In *Drosophila melanogaster* lab populations, for example, the X chromosome was estimated to harbor 97% of the genomewide sexually antagonistic variation, corresponding to 45% of the genomewide variation in fitness, whereas only 20% of the euchromatic genome is X linked in *Drosophila* (Gibson et al. 2002).

The difference between the evolutionary contexts that the sex chromosomes and the autosomes provide for sexually antagonistic alleles helps to explain why sex chromosomes are unusual with respect to gene content and patterns of sex-biased gene expression across a wide range of species (Rogers et al. 2003; Vallender & Lahn 2004; Kaiser & Ellegren 2006). The nonrecombining region of the human Y chromosome, for example, features only a few genes, which frequently are involved in male-specific functions such as spermatogenesis and sex determination (Lahn et al. 2001). The human X chromosome is enriched for genes involved in sex and reproduction, brain-related functions, and skeletal muscle expression (Hurst & Randerson 1999; Saifi & Chandra 1999; Zechner et al. 2001; Lercher et al. 2003; Ross et al. 2005; Vallender et al. 2005; Skuse 2006). In mice, genes preferentially expressed in ovary, placenta, or early spermatogenesis are overrepresented on the X chromosome, whereas genes expressed during late spermatogenesis are nearly absent (Wang et al. 2001; Khil et al. 2004; Divina et al. 2005), presumably in response to (or allowing for) early X inactivation during spermatogenesis (Betrán et al. 2002; Wu & Xu 2003). In *Caenorhabditis elegans*, by contrast, genes expressed in the spermatogenic and oogenic cells are underrepresented on the X chromosome (Reinke et al. 2004), and the X chromosome of *Drosophila* appears to be a disfavored location for genes with male-biased expression (Parisi et al. 2003; Ranz et al. 2003).

Clearly, and particularly for the X chromosome, the observations are not consistent across species. Several explanations have been offered to account for this fact (Rogers et al. 2003; Oliver & Parisi 2004; Vallender & Lahn 2004). The consequences of sexual conflict for the functional and expression bias of genes on the sex chromosomes are inherently difficult to predict because the bias resulting from sexual conflict could go either way, depending on the dominance of sexually antagonistic alleles (Rice 1984). Little is known about the distribution of dominance coefficients for new sexually antagonistic mutations and whether this distribution is similar across species. Moreover, the importance of the more frequent presence of the X chromosome in females (favoring dominant female-benefit alleles) relative to the effect of hemizygous exposure of the X chromosome in males (favoring recessive male-benefit alleles) will vary with the age of the sex chromosomes (Oliver & Parisi 2004). Hemizygous exposure will be less prevalent in species with young sex chromosomes, where the Y chromosome has not yet lost all its genes. Finally, constraints induced by the particular mechanism of dosage compensation in a given species, and the presence or absence of germline X

inactivation or gene transposition biases, may help to explain some of the observed differences between species. Recent studies focusing on the Z chromosome in birds (Kaiser & Ellegren 2006; Storchová & Divina 2006) provide interesting comparative data that may help to disentangle the consequences of the multitude of evolutionary processes that have shaped the sex chromosomes.

Consequences of Intralocus Conflict for Mate Choice

A gene involved in sexual selection is likely to have had sexually antagonistic fitness effects at some point in its evolutionary past, or it may even presently have such effects (e.g., Price & Burley 1994; Björklund & Senar 2001; Robinson et al. 2006; Mank 2007). One would therefore expect the genomic distribution of sexually selected traits to reflect the same bias toward location on the sex chromosomes as can be observed for sexually antagonistic genes in general (Gibson et al. 2002). Several authors have explored the location of sexually selected genes and found significant sex linkage. From a compilation of data from insects and mammals, Reinhold (1998) estimated that one-third of the phenotypic variation in sexually selected traits is caused by X-chromosomal genes in species with male heterogamety. Lindholm and Breden (2002) provide a review of sexually selected traits in guppies. Only two of these traits are autosomal, 16 are Y linked, 24 recombine between the X and the Y, and two are X linked. At a more detailed scale of analysis, several studies provide examples of specific sexually selected loci that are located on the sex chromosomes (e.g., Kallman 1970; Wada et al. 1998; Lande et al. 2001; Lindholm & Breden 2002; Streelman et al. 2003; Fernandez & Morris 2008). Evidence for the sex linkage of sexually selected traits is not unequivocal, however. Fitzpatrick (2004) suggested that pleiotropic gene effects may prevent the loss of sexually selected (and presumably sexually antagonistic) genes from the autosomes, which would considerably reduce biases in the genomic location of sexually selected genes. His survey of sexually selected genes in *Drosophila melanogaster* indicated that most of these genes have pleiotropic effects and revealed no evidence for preferential sex linkage.

From a theoretical perspective, sex linkage of genes affecting male display traits or female preferences has important consequences for the genetic association between these genes. Nonrandom mating creates a genetic correlation between preference and display traits, which is instrumental in driving Fisher's runaway process (Fisher 1958) or the sexual selection of good genes (Hamilton & Zuk 1982). The strength of this correlation depends on patterns of sex linkage (Kirkpatrick & Hall 2004). Under some kinds of sex linkage (e.g., Z-linked preferences) a Fisherian runaway is more likely than under autosomal inheritance, whereas under others (e.g., X-linked preferences and autosomal displays) the good-gene process is more powerful. Different sex chromosome systems are also associated with different probabilities for the random loss of rare trait and preference alleles. Rare alleles are better protected against loss in species with ZZ/ZW sex determination (Reeve & Pfennig 2003).

A third, and more direct, effect of sexual antagonism on sexual selection applies when females exert a preference for a trait that is expressed in both sexes. Sexual antagonism can maintain additive variation in such a trait but at the same time fully erode any genetic benefit of mate choice (Kirkpatrick & Hall 2004; Brommer et al. 2007; Radwan 2008). This is because sexual antagonism interferes with the reliable transmission of genetic benefits from one generation to the next. Seger and Trivers (1986) were the first to demonstrate theoretically that female mating preferences should evolve to favor males who exhibit variants of the trait that confer low fitness on sons but high fitness on daughters. Patterns of sex linkage can qualitatively affect this result. In species with a Z-linked trait, females more often evolve mating preferences for males

carrying alleles beneficial to sons (Albert & Otto 2005).

Empirical studies have confirmed that sexual antagonism can strongly interfere with adaptive mate choice, as suggested by the theory just reviewed. Female mating preference in the southern ground cricket *Allonemobius socius* has sexually antagonistic consequences for offspring fitness. Successful males produced sons with a higher mating success but daughters with a lower than average reproductive success (Fedorka & Mousseau 2004). Pischedda and Chippindale (2006) observed similar effects in *Drosophila melanogaster* lab populations. High-fitness mothers produced daughters that were more fit than the daughters produced by low-fitness mothers, but they produced sons that were less successful. The daughters of low-fitness males were more successful than the daughters of high-fitness males, and paternal fitness had no significant effect on the fitness of sons. The latter finding was explained by the fact that a major part of fitness variation in *Drosophila* is X linked (Gibson et al. 2002); males do not transmit their X chromosome to their sons.

If these patterns are typical, a female that chooses to mate with a successful male will gain no indirect genetic benefit through sons and incur a fitness loss in the reduced fitness of daughters. In fact, any form of mate choice on males on the basis of sexually antagonistic variation in species with male heterogamety will result in a regression of fitness to the mean (Pischedda & Chippindale 2006). In species with female heterogamety, sexual selection is not disrupted by the inability of males to transmit preferred sex-linked sexually antagonistic variation to their sons. This is one of several factors that may explain why species with female heterogamety (including birds and butterflies) seem to have evolved more elaborate sexual displays (Reeve & Pfennig 2003).

Sex Determination

Intralocus sexual conflict not only shapes the gene content of the sex chromosomes but also affects sex determination, the process that led to the evolution of sex chromosomes in the first place. The mechanisms of sex determination are remarkably diverse. Several clades show evidence of frequent and rapid evolutionary changes in sex determination (Bull 1983; Marín & Baker 1998; Haag & Doty 2005). The broadest categories of sex determination are environmental sex determination (ESD), in which the sex of an individual is determined during early development by an environmental cue (e.g., temperature), and genetic sex determination (GSD), in which the sex of an individual is determined entirely by its genes. The phylogenetic distribution of ESD and GSD suggests that many evolutionary transitions between both types of sex determination have occurred (Charlesworth 2002; Kraak & Pen 2002) and several examples of intermediate forms between ESD and GSD are known (e.g., Girondot et al. 1994). ESD is likely to appear when there is environmental variation with sufficiently strong differential fitness effects on the sexes (Charnov & Bull 1977). GSD will tend to be favored over ESD when early sex determination is developmentally advantageous, when ESD leads to excessive fluctuations in the population sex ratio (Bulmer & Bull 1982; Van Dooren & Leimar 2003) or when there is genetic variation that differentially favors males and females (Rice 1986). The latter possibility suggests that sexually antagonistic variation can induce evolutionary transitions from ESD to GSD. All else being equal, a sex-determining gene will tend to increase in frequency when it is closely linked to a gene with beneficial effects in the sex that the sex-determining gene tends to produce. Similarly, GSD can be selected for when the sex-determining gene has favorable sex-specific pleiotropic fitness effects (Kraak & de Looze 1993; Kraak & Pen 2002).

It has often been assumed that transitions between GSD systems require an intermediary phase of ESD, but several peculiar forms of sex determination can be explained as transitional forms between standard dual sex chromosome systems (Bull 1983). Indeed, detailed studies of

several genera suggest that transitions between different types of GSD can occur directly. In the cichlid genus *Tilapia* and its close relatives, for example, sex is determined by two unlinked loci, one of which is XY and the other, ZW. Sex is determined by the XY system in some species and by the ZW system in others, whereas in at least one species (*Oreochromis aureus*) both loci are variable and contribute to sex determination (Cnaani et al. 2007). Also, the genus *Xiphophorus* (platyfish and swordtails) includes species with XY and ZW sex determination; *Xiphophorus maculatus* is polymorphic for both (Volff & Schartl 2001, 2002).

Groups such as mammals and birds feature advanced sex chromosomes that have evolved mechanisms for dosage compensation and accumulated a significant fraction of the genomewide sexually antagonistic variation. Interference with sex determination in these groups is likely to have severe negative consequences, which would counteract the invasion of novel sex factors on the autosomes. Major rearrangements of genes mediated by fusions or translocations between the sex chromosomes and autosomes have been observed in several species (Charlesworth & Charlesworth 2005), and it is conceivable that such chromosomal rearrangements can open the door to changes in the sex determination system even in species with well-differentiated sex chromosomes. Nevertheless, the most compelling evidence for evolutionary transitions between genetic sex determination systems comes from species with relatively young sex chromosomes. Amphibians and reptiles show evidence of recent and rapid changes between male and female heterogamety (Hillis & Green 1990; Ezaz et al. 2006) and a phylogenetic analysis of genetic sex determination in the teleost fishes found that eight of 26 families include species with XY and with ZW sex determination (Mank et al. 2006). At least four different chromosomes determine sex in different species of salmon (Woram et al. 2003).

Evolutionary transitions between different types of GSD can be explained by a theoretical argument that is in essence similar to the one given earlier for transitions between ESD and GSD. If there are no inherent fitness differences between sex determination genotypes, then transitions between different types of GSD are selectively neutral (Bull & Charnov 1977; Bull 1983). Plotted in the space of genotype frequencies, a curve of neutrally stable equilibria connects the alternative types of GSD, and the sex ratio at all points along the curve is 1:1 (Bull & Charnov 1977). Linkage of sexually antagonistic loci with one of the sex determination factors provides a deterministic force that pushes the gene frequencies along the curve toward the GSD mechanism that is associated with the sexually antagonistic variation. Rice (1986) used this line of reasoning to argue for the instability of polygenic sex determination by showing that a novel, major sex-determining gene linked to a sexually antagonistic allele can invade a population with polygenic sex determination and induce a transition from polygenic to genic sex determination.

Transitions between different types of GSD are slightly more complicated when both the novel and the ancestral sex determination loci are genetically associated with sexually antagonistic alleles, as one would typically expect in cases where existing sex chromosomes are replaced by a novel sex determination system. Van Doorn and Kirkpatrick (2007) analyzed this scenario, focusing on the invasion of a neo-Y chromosome in a population with XX/XY sex determination. In general, whichever sex determination allele is more strongly associated with sexually antagonistic variation will prevail, but when the linkage between sex determination alleles and sexually antagonistic alleles is tight, bistability (favoring whichever sex determination system was established first) and a protected polymorphism of sex factors are possible alternative evolutionary outcomes.

It is still an open question to what extent sexual antagonism is responsible for the apparent evolutionary lability of sex determination relative to alternative mechanisms, such as genetic drift (Bull & Charnov 1977),

meiotic drive (Werren & Beukeboom 1998), or sex ratio selection (Kozielska et al. 2006). A growing number of examples of recently derived sex chromosomes that carry sexually selected loci (Kallman 1970; Wada et al. 1998; Lande et al. 2001; Lindholm & Breden 2002; Streelman et al. 2003; Fernandez & Morris 2008) suggest that sexual antagonism may be involved; the sexual conflict hypothesis predicts that recently derived sex-determining regions will be associated with genes that are targets of sexually antagonistic selection. A stringent test of the hypothesis would be to look for sexually antagonistic genes in very young sex chromosomes and in the homologous autosomal regions of closely related species that still use the ancestral sex-determination system. Promising systems for these investigations include the medaka (Matsuda 2005) and the three-spined stickleback (Peichel et al. 2004).

Conclusion and Perspective

That females and males experience opposing selection pressures across a wide variety of traits has long been realized (Fisher 1958; Parker 1979), but it has only more recently become clear how ubiquitous sexual antagonism is. One important reason for this is that rigorously demonstrating sexually antagonistic variation requires sophisticated techniques that are available only for well-studied lab species. Experimental studies on *Drosophila melanogaster* lab populations (Rice 1992, 1998b; Chippindale et al. 2001; Gibson et al. 2002; Prasad et al. 2007; Morrow et al. 2008) have provided compelling evidence for the existence of substantial genomewide sexually antagonistic variation. Comparative analyses of genomewide gene expression profiles in *Drosophila* show that sex-specific gene regulation patterns can evolve rapidly (Ranz et al. 2003). This finding suggests that sexually antagonistic selection is highly dynamic. If it were not, intralocus conflict presumably could quickly be resolved by the evolution of sexual dimorphism, and a negative intersexual correlation for fitness would not persist. That being said, the understanding of the resolution of intralocus conflict is far from complete, and it is not sufficiently clear how sex-specific regulation evolves for genes that are under sexually antagonistic selection (Mank 2009). An improved understanding of the different time scales that are involved in the emergence of intralocus sexual conflict (through fluctuating selection pressures, mutation, or epistatic interactions with other evolving genes) and its resolution (through translocation, gene regulation, and other mechanisms of sex-specific epistasis) is crucial to appreciate the relative importance of selection and constraint in the context of sexual conflict.

The few observations of negative intersexual correlations for fitness in the wild (Foerster et al. 2007; Brommer et al. 2007) strongly suggest that the relevance of intralocus sexual conflict extends beyond the idealized lab environment. However, more studies on natural populations are needed to assess the evolutionary significance of intralocus conflict under natural conditions. There are still relatively few studies that cleanly demonstrate sexually antagonistic selection in the field, and it is currently not clear how much of the variation in fitness in natural population is attributable to unresolved sexual conflict. If intralocus conflict is as essential as the lab studies suggest (Chippindale et al. 2001), then this would have obvious implications for the maintenance of genetic variation in wild populations, the lek paradox, and sexual selection on good genes, which all have been extensively studied in the field.

For a final point: many of the evolutionary implications of intralocus conflict that were discussed in this review do not rely on sexually antagonistic variation in the strict sense. A negative genetic correlation for fitness can exist only with segregating sexually antagonistic variation. In this respect, negative correlations provide crucial evidence for the widespread occurrence of sexually antagonistic alleles. However, what matters qualitatively for most of the potential implications of intralocus

conflict is that the correlation for fitness between the sexes is less than +1. Sexually antagonistic alleles are highly effective but not required to generate deviations from a perfect positive genetic correlation between the sexes. Sex-limited expression can reduce the correlation to zero and even alleles with beneficial or deleterious effects in both sexes can contribute to a reduction of the intersexual correlation for fitness. For example, a deleterious allele with different negative fitness effects in females and males that is maintained through mutation–selection balance, pleiotropic frequency dependence, or gene flow between populations will affect the genetic load of males and females differently. The widespread occurrence of such alleles throughout the genome would qualitatively affect the gene content of the sex chromosomes, the stability of sex determination systems, or the genetic benefits of mate choice in the same way as the presence of strictly sexually antagonistic variation. This assertion suggests that the presence of a negative intersexual genetic correlation for fitness is perhaps too stringent a criterion to conclude that intralocus sexual conflict is worthy of consideration as an explanatory framework.

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Conflicts of Interest

The author declares no conflicts of interest.

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