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SYMPOSIUM

The Genomics of Sexual Conflict*

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ABSTRACT: Sexual dimorphism is a substantial contributor to the diversity observed in nature, extending from elaborate traits to the expression level of individual genes. Sexual conflict and sexually antagonistic coevolution are thought to be central forces driving the dimorphism of the sexes and its diversity. We have substantial data to support this at the phenotypic level but much less at the genetic level, where distinguishing the role of conflict from other forms of sex-biased selection and from other processes is challenging. Here we discuss the powerful effects sexual conflict may have on genome evolution and critically evaluate the supporting evidence. Although there is much potential for sexual conflict to affect genome evolution, we have relatively little compelling evidence of a genomic signature of sexual conflict. A central obstacle is the mismatch between taxa in which we understand sexually antagonistic selection and those in which we understand genetics.

Keywords: sexual conflict, sexually antagonistic selection, genomics.

Introduction

The sexes share much of the same genome and share phenotypic interactions, not the least of which is mating. Yet they also differ in their evolutionary interests, in a large part due to anisogamy, which can have cascading effects throughout their life history (Parker 1979, 2006; Schärer et al. 2012). The fact that the evolutionary interests of the sexes differ is evident in the remarkable sexual dimorphism that is characteristic of most groups, and this diversity motivated Darwin's (1871) sister theory to natural selection—sexual selection. Sexual reproduction between these differently selected types, males and females, leads to two different challenges: the requirement for individuals of opposite sex to interact to reproduce (without having identical interests) and the requirement to develop two different phenotypes (males and females) using largely the same set of genes. These challenges can lead to conflict between the sexes, and sexually antagonistic selection has the potential to shape genomes in interesting ways. Here we critically evaluate the evidence for these conflicts between sexes in shaping genome evolution. We discuss the two broad classes of conflict, inter- and intralocus conflicts, and their expected signatures in the genome. Throughout, we emphasize the importance of understanding the nature of selection in distinguishing sexual conflict from other processes that may have similar impacts on the genome.

Interlocus Sexual Conflict

In interlocus conflict, there is sexually antagonistic selection on an interaction between the sexes that is mediated by separate loci in each sex. Parker (1979) and others recognized that the divergent interests of the sexes meant that there may often be conflicts over their reproductive interactions (Rice and Holland 1997; Arnqvist and Rowe 2005; Rice and Gavrilets 2014). One example is mating rate, where optimal rates may be higher in one sex (often males) than the other, leading to conflicts. A straightforward way to capture this conflict is to frame it in terms of phenotypic selection—there is sexually antagonistic selection on mating rate (Rowe and Day 2006). Any male traits that increase the bearer's mating rate are favored in males but directly reduce the fitness of interacting females (these traits are sexually antagonistic), whereas any female traits that decrease mating rate are favored in females but detrimental to male fitness. One outcome of sexually antagonistic selection is an exaggeration and diversification of the traits that are subject to it, leading to the evolution of sexual dimorphism and sexually dimorphic trait diversity. Theory suggests that the evolutionary consequences of antagonistic selection can also lead to a variety of other important evolutionary outcomes, including peak shifts, speciation, a reshaping of the genetic architecture of the traits involved, increased variance in fitness, and reduced population fitness (Rice and Holland 1997; Arnqvist and Rowe 2005; Rice and Gavrilets 2014).

This form of coevolution between the sexes shares many conceptual similarities with host-pathogen coevolution, though the two literatures have developed largely independently (Brockhurst et al. 2014; Kasimatis et al. 2017; see also Chapman 2018).

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In the host-pathogen literature, two major types of coevolutionary dynamics are recognized (Agrawal and Lively 2002; Boots et al. 2014). In arms race dynamics, both players evolve enhanced or alternative traits that advance their interest. Genetically, this means a constant turnover of alleles at one or more loci, with more derived alleles being superior to ancestral ones. At the phenotypic level, this could be manifest as the escalation of armaments used in sexually antagonistic interactions (e.g., grasping and antigrasping structures in some insect groups; Arnqvist and Rowe 2002; Bergsten and Miller 2007). In an arms race, it is easy to imagine a never-ending escalation of armaments, giving rise to many selective sweeps. However, the ecological and physiological costs of such traits can limit escalation in one or both sexes, and under some conditions de-escalation is possible (Gavrilets et al. 2001; Rowe et al. 2005). It is also possible that environmental changes may add new costs that force the de-escalation of such traits, driving a new set of selective sweeps.

Arms race coevolution has dominated thinking in the sexual conflict literature since Parker's first conflict models (Parker 1979). An alternative form of coevolution, well recognized in the host-pathogen literature, is Red Queen dynamics. This form of coevolution is based on the idea that one type of player must match the other's trait to win the contest, while the other type wins by avoiding a match. This leads to a case where one player chases the other through genotypic space. From the perspective of one player type, no genotype is inherently better than another; the success of a genotype depends on the genotype of the other type of player. Genotypes that were successful in the past but unsuccessful at present can be successful again at some future time as a result of coevolution. This nontransitivity means that alleles can be recycled, possibly leading to the long-term maintenance of polymorphisms.

Arms race and Red Queen dynamics should leave different signatures of molecular evolution. Loci characterized by arms race dynamics should display signals of selective sweeps (e.g., reduced levels of neutral diversity around selective targets). In contrast, if Red Queen dynamics result in negative frequency dependence that maintains alternative alleles over long periods, then such loci display evidence of balancing selection (e.g., elevated levels of neutral variation around targets of selection). However, neither signature is completely unique. Loci affecting traits involved in sexual arms races may eventually fall under balancing selection if natural selection restrains further escalation of sexually selected traits. Conversely, Red Queen dynamics, especially in finite populations, may result in extreme swings in allele frequency, resulting in fixations.

Evidence for Interlocus Conflict and Sexually Antagonistic Coevolution in the Genome

A direct approach to identifying the signature of sexual conflict in the genome is to first identify sexually antagonistic traits and then ask if they leave the expected patterns in the genome. Identifying a trait as sexually antagonistic requires demonstrating that selection in one sex is antagonistic to fitness in the other sex; that is, traits favored in females reduce the fitness of the males they interact with (Rowe and Day 2006). Sexually antagonistic coevolution describes the intersexual coevolution of these sexually antagonistic traits (Rice and Holland 1997; Arnqvist and Rowe 2005; Rice and Gavrilets 2014). Sexual conflict over mating rate is illustrative of the relationship between sexually antagonistic traits and coevolution. Consider a trait expressed only in males that increases mating rate and a trait expressed only in females that helps females avoid unwanted matings. Such traits are sex limited in expression and thus not under antagonistic selection sensu stricto, which requires selection of opposite direction in the two sexes, but these traits are considered sexually antagonistic because the traits benefit the individuals of the expressing sex to the detriment of individuals of the opposite sex with whom the expressing sex interact.

There are numerous traits that appear to be sexually antagonistic, though just a few very well supported examples of sexually antagonistic coevolution at the phenotypic level (Fricke et al. 2009; Perry and Rowe 2014) and even fewer clear examples of rapid molecular evolution driven by sexually antagonistic coevolution. Perhaps the best potential genetic example of this kind of coevolution comes from proteins mediating sperm-egg interactions (Levitan and Ferrell 2006; Findlay and Swanson 2010; Vacquier and Swanson 2011; Wilburn and Swanson 2016). Here, the proposed conflict is over polyspermy, with sperm favored to increase fertilization probability and eggs favored to guard against multiple fertilizations. Pairs of interacting proteins on male and female gamete surfaces have been identified, and both are evolving extremely rapidly. However, in some cases, alternative mechanisms for these observations, including sperm competition, cannot be ruled out (Wilburn and Swanson 2016).

Much attention has been given to the role of *Drosophila* seminal fluid proteins (SFPs) in sexual conflict (Sirot et al. 2014; Chapman 2018). Several of the genes encoding these proteins show rapid evolution (Aguade et al. 1992; Swanson et al. 2001), and this has been interpreted as resulting from sexual conflict (Sirot et al. 2014). However, of the multitude of SFPs, only one (sex peptide, SP) is known to harm females (Wigby and Chapman 2005) and this only under some environmental conditions (Fricke et al. 2010). Moreover, although the female receptor for sex peptide is known (sex peptide receptor, SPR; Yapici et al. 2008), SPR itself appears relatively conserved and it is not known whether the evolution of SP in males is driving evolutionary responses of SPR in females, or vice versa (Sirot et al. 2014). Many of these SFPs are known to influence sperm competition, and their evolution may therefore be driven by male-male competition rather

than sexual conflict. One can imagine cases in which females represent an environment within which males compete, and it is this competition among males that primarily drives evolutionary change in SFPs. Alternatively, if evolution in males has some detrimental consequences for females (e.g., altering mating rates), females may respond to these costs, initiating sexually antagonistic coevolution. Distinguishing the extent to which coevolution is responsible for rapid change will require more attention to understanding the mechanisms and economics of interactions between male and female genes, especially on the female side.

In sum, perhaps the best examples of interlocus conflict at the genetic level come from reproductive proteins, but even here the evidence of sexually antagonistic selection shaping genomic evolution is not yet compelling (see above). We are left in a position where genetic data are poor for those traits where there is strong support for sexually antagonistic coevolution and evidence of sexually antagonistic coevolution is weak or absent in those traits where we have a good understanding of the genetics. One obvious path forward is to extend the early work on sex peptide—both studies of selection and molecular evolution—to the dozens of other SFPs that may be antagonistic. In other cases where sexually antagonistic phenotypic traits are known, genetic dissection of those traits would allow for an illuminating comparison of rates and patterns of molecular evolution between genes underlying the male and female components of sexually antagonistic selection. One recent example is a study of the elaborated grasping male antennae of the water strider *Rheumatobates rylei*. Khila et al. (2012) compared transcriptomes from male and female developing larvae to identify candidate genes involved in the elaboration of these traits and then tested them with RNA interference. The results demonstrated that a short isoform of the patterning gene, *distal-less* (*dll*), was responsible for the fine-scale elaboration of the male antennae. There is now the opportunity to study the evolution of this gene and the relevant gene networks underlying this antagonistic trait.

Another avenue of interest is to study the consequences of known antagonistic traits on the genome in real time. Male mating harassment of females (by definition) causes a direct reduction in female fitness and, when directed toward a subset of females, may alter the strength of selective differences among females. Long et al. (2009) demonstrated that male *Drosophila* preferentially harass the best-quality females, reducing the difference in fitness between high- and low-quality females (i.e., weakening selection on overall female quality). Based on this, Arbuthnott and Rundle (2012) inferred that biased harassment impeded the purging of deleterious visible mutations in experimental populations of *Drosophila melanogaster*. In an "evolve and resequence" study with *Drosophila serrata*, Chenoweth et al. (2015) found that SNP frequency change accompanying adaptation to a novel environment was significantly altered in the experimental treatments that manipulated the potential for male harassment of females. Intriguingly, SNPs that appeared adaptive when the opportunity for harassment was low did not respond or sometimes reversed their direction of change when harassment was maximal. Together, these studies illustrate how male harassment has genome-wide evolutionary consequences by slowing the purging of deleterious alleles and reducing the rate of adaptation. However, it is easy to imagine the opposite outcome. If high-quality females were less affected by harassment than low-quality females, then harassment would exaggerate the fitness differences between high- and low-quality females, making selection stronger. Recent experiments indicate that males may either increase or decrease selection on females depending on the physical environment in which mating interactions occur (Yun et al. 2017; see also Colpitts et al. 2017; Singh et al. 2017).

Evolution in Males versus Females

In general, there is more evidence for rapid sequence and regulatory evolution of male-biased genes than female biased-genes (Parsch and Ellegren 2013; Ingleby et al. 2015). Similarly, in sexually antagonistic phenotypic traits, there often appears to be more rapid divergence in male traits and little evidence of a response in interacting female traits (Arnqvist 2006; Fricke et al. 2009; Perry and Rowe 2014). How should we interpret this in a coevolutionary framework? One possibility is that, over time, males are getting increasingly better at exploiting females. Perhaps male-biased genes are less constrained, and this would allow rapid evolution of males relative to females. Spatial and temporal expression is narrower for male-biased genes, many of which tend to be expressed primarily in the testis, whereas expression in female-biased genes is often more widespread (Zhang et al. 2007). Male-biased genes are often duplicates and of recent origin (Gallach et al. 2010; Wyman et al. 2012). Finally, there is some evidence that male-biased genes tend to be more tissue-specific and less networked than female-biased genes (Assis et al. 2012; Hansen and Kulathinal 2013). Each of these factors suggest that male-biased genes may be less constrained by pleiotropy than female-biased or unbiased genes.

This lack of constraint on males in itself would lead to fast evolution. However, under interlocus sexual conflict, this would lead to a continued decline in female fitness, perhaps resulting in population collapse. Alternatively, males and females coevolve, but each genetic change in females is countered by many genetic changes of smaller effect in males. However, the simplest interpretation is that much of the rapid sequence evolution in male-biased genes is not driven by antagonistic coevolution but is a result of standard sexual selection (male-male competition and female choice). Sexual selection can lead to rapid divergence in males without a concomitant effect on females, if females have nonevolving pref-

erences to which males are continually refining their traits (Arnqvist 2006). The observation of rapid male sequence evolution in flies mimics the observation of rapid phenotypic divergence of male traits in many other taxa (e.g., birds, fish, insects). How much of this divergence is attributable to antagonistic coevolution rather than other forms of sex-specific selection is an open question (Arnqvist and Rowe 2005; Rice and Gavrilets 2014).

Intralocus Sexual Conflict

A second form of sexual conflict is intralocus conflict, which describes sexually antagonistic selection on a trait where, in contrast to interlocus conflict, the trait is shared by the sexes and has a shared genetic basis (Rice and Holland 1997). Males and females differ in many and often spectacular ways, implicating a history of differential selection between the sexes. Much as the natural historians of the past noted sexual dimorphism in phenotypes, the genomicists of today have described remarkable dimorphism in the transcriptome. Studies across a variety of taxa suggest a large fraction of genes have sex-biased expression in some tissues at some ontogenetic stages (e.g., Parsch and Ellegren 2013; Ingleby et al. 2015). While caution is needed in interpreting expression data (see below), these observations suggest a history of divergent selection between the sexes on gene expression. On the other hand, the existence of dimorphism suggests that intralocus conflict can be resolved, at least to some extent. Yet, while it persists, intralocus conflict may shape patterns of genetic variation within populations and the genetic architecture of adaptive differences between species.

Genetic Variance in Fitness

Intralocus sexual antagonism can maintain genetic variation in fitness. In some cases, sexual antagonism can result in balancing selection, whereby selection alone maintains polymorphism. This requires particular types of dominance relationships and can be facilitated by alleles locating on a sex chromosome (Rice 1984; Fry 2010; Arnqvist et al. 2014). Even if the appropriate conditions are not met for true balancing selection, sexual antagonism can slow the loss of alleles experiencing net directional selection and elevate the genetic variance in fitness at mutation-selection balance (Connallon and Clark 2014). The extra variation arising from sexual antagonism can fuel response to adaptive opportunities, including peak shifts (Lande and Kirkpatrick 1988; Bonduriansky 2011), because more fitness-affecting polymorphisms persist in populations and at higher allele frequencies. It is unknown how much intralocus sexual antagonism contributes to levels of standing genetic variation, but some studies suggest it is an important factor (e.g., Chippindale et al. 2001; Qvarnström et al. 2006; Delcourt et al. 2009; Mokkonen et al. 2011).

Variation maintained by intralocus conflict is expected to ultimately result in a negative genetic correlation in fitness between the sexes, as unconditionally beneficial (deleterious) alleles are more quickly fixed (purged), leaving behind those with sexually antagonistic effects. Such a pattern was first clearly demonstrated in a laboratory fly population in which haplotypes that yielded high fitness in males also resulted in low fitness in females (Chippindale et al. 2001), and much of this variation was localized to the X (Gibson et al. 2002). Since then, negative intersexual genetic correlations have been reported in several other systems, including wild populations (Poissant et al. 2009). Although negative intersexual genetic correlations are the hallmark of intralocus conflict, the lack of such a correlation (or even a positive one) does not imply the absence of intralocus conflict. Variation at loci that affect both sexes concordantly can swamp out negative covariance created by loci under intralocus conflict. This logic mirrors early arguments about the difficulty in detecting antagonistic pleiotropy by examining genetic correlations among life-history traits (Van Noordwijk and de Jong 1986; Houle 1991).

An alternative approach to detecting sexually antagonistic variation is to use experimental evolution. Following on classic experiments by Rice (1996, 1998), Prasad et al. (2007) used the genetic tools of *Drosophila* to allow selection on genomes in males only, experimentally removing any opposing selection in females. Populations evolving in this manner resulted in genotypes that yielded high-fitness males but low-fitness females. These changes occurred in only 25 generations, suggesting that selection was able to make use of antagonistic alleles present in standing variation to create substantial phenotypic change.

The existence of negative intersexual genetic correlations in some populations and the evidence from experimental evolution studies both suggest there is sexually antagonistic variation segregating within populations. However, it remains largely unknown what fraction of the variation can be attributed to sexual antagonism and why populations differ in the contribution of sexual antagonism to total fitness variance. At equilibrium, one might expect a high fraction of variance is due to sexual antagonism because variants with concordant effects will be fixed or eliminated, with only low levels maintained by mutation-selection balance. However, in the wild, populations are often displaced from optima by shifting environments or gene flow from alternative habitats. In this case, we would expect to find more concordant variation. Recent theory has confirmed this general logic (Connallon and Clark 2014) and indicates that sexual antagonism, of at least some degree, is inescapable whenever a species with two sexes undergoes adaptation. In fly populations adapted to a specific laboratory environment, Long et al. (2012) found that successful males sired daughters that were less fit than those of unsuccessful males, consistent with a heavy influence of sexual antagonism. In populations that were not adapted to this

environment, successful males sired more fit daughters, suggesting more of the variation in these nonequilibrium populations was sexually concordant. By contrast, direct comparison of intersexual genetic correlations between ancestral and stressful environments has thus far revealed mixed results, with the correlation sometimes increasing as expected (Berger et al. 2014) but in other cases becoming more negative (Delcourt et al. 2009).

If sexual antagonism maintains variation, then we would expect to find the signatures of balancing selection in genome scans, but there is scant evidence of this. Most good examples of balancing selection are associated with disease-related genes (Tian et al. 2002; Andres et al. 2009), where the ecological source of balancing selection is more likely to be host-parasite coevolution than intralocus sexual antagonism. However, signatures of balancing selection are notoriously difficult to detect. Further, recent theory has emphasized that in many cases where sexual antagonism would maintain variation in infinite populations, such polymorphisms will be lost through drift before the expected signatures of long-term balancing selection arise (Connallon and Clark 2012). Alternatively, conflict at such loci eventually gets resolved (see below) so that polymorphisms are not maintained indefinitely. Nonetheless, signatures of balancing selection, even if weak on their own, can be combined with other evidence of sexual antagonism to help refine searches for sexually antagonistic variants (Mank 2017*a*).

In sum, multiple approaches—quantitative genetics, experimental evolution, expression analysis, sequence analysis—are being used to assess whether sexual antagonism contributes to genetic variance in fitness. Each approach provides a different type of perspective, and so far, there is no clear picture. Data from some quantitative genetic analyses, experimental evolution studies, and studies of selection on expression indicate that there is standing genetic variation for intralocus sexual antagonism. However, there is still much to learn. What types of genetic pathways tend to harbor segregating sexually antagonistic variation? Is sexually antagonistic variation typically due to structural or regulatory variants? What is the timescale over which such polymorphisms persist? When such polymorphisms are lost, why so (i.e., resolution of conflict, drift, or change in selection)? How often is sexually antagonistic variation generated by mutation (i.e., mutational target size)? Even though there are multiple types of evidence for standing variation for intralocus sexual conflict, there are no convincing estimates of how much sexually antagonistic alleles contribute to either sequence diversity or fitness variation. A major outstanding challenge—which is possible to address with a combination of genomics and rich fitness data sets—is to identify sexually antagonistic variants and estimate how much of the heritability of fitness they can explain. Of course, the primary challenge is to identify the sexually antagonistic variants, and few have been identified so far.

Sexually Antagonistic Polymorphisms

Thus far only a handful of studies have identified sexually antagonistic polymorphisms at the genomic resolution of individual genes. These include insecticide resistance in *Drosophila melanogaster*, which is controlled by the cytochrome p450 gene *Cyp6g1* (Smith et al. 2011; Rostant et al. 2015; Hawkes et al. 2016); the *Pax7* locus, which controls antagonistic orange-blotch coloration in cichlids (Roberts et al. 2009); and *VGLL3*, which underlies variation in age at maturity in Atlantic salmon, which experiences sexually divergent selection (Barson et al. 2015). While single gene studies cannot by themselves inform us of general patterns, even the small number conducted to date have led to new insights. For example, the two fish studies each indicate a different genomic mechanism by which sexual antagonism might be resolved.

Sexual antagonism over orange-blotch color variation in cichlids is generated by a regulatory mutation in the *Pax7* gene. Here orange-blotched (OB) coloration is adaptive for females, where it enhances crypsis, but the blotching reduces male fitness because it obscures nuptial coloration, which is important for mating success (Roberts et al. 2009). Interestingly, the authors found that the sexually antagonistic *OB* haplotype is tightly linked to a dominant female sex-determination locus. This genomic colocalization effectively mitigates the conflict by linking the female-beneficial OB allele to the production of females, a finding that is consistent with theory that links the evolution of sex chromosomes to sexual antagonism (Van Doorn and Kirkpatrick 2007).

In Atlantic salmon (*Salmo salar*), age (and size) at maturity is subject to sexually divergent selection, with early maturity favored in males and later maturity favored in females. Barson and colleagues (2015) found that a variant in the vestigial-like family member 3 gene (*VGLL3*) explained an unexpectedly large fraction of the phenotypic variance in age at maturity. Intriguingly, segregating variation at this major-effect locus exhibited sex-dependent dominance reversal, with male and female heterozygotes displaying early and late maturation, respectively. Sex-specific dominance reversals are predicted to be favored under sexually antagonistic selection as they mitigate allele-sex mismatches, allowing sexually antagonistic polymorphisms to be maintained in populations (Spencer and Priest 2016).

Though much attention is given to the idea of sexually antagonistic alleles that maintain genetic variation, most sexually antagonistic (SA) alleles are probably either lost or fixed. Theoretical analyses (Connallon and Clark 2012) point out that this is because most SA mutations will be either (i) deterministically unstable because beneficial effects in one sex outweigh negative effects in the other or (ii) under sufficiently weak balancing selection that they will be lost or fixed by genetic drift. However, little is known about the extent to which sexual antagonism contributes to fixed differences be-

tween populations or closely related species. One approach might be to examine the intersexual genetic covariance in late-generation hybrids (e.g., F_4) from crosses between isolated populations or closely related species. If alternative sexually antagonistic alleles are fixed between populations, then there should be a larger, more negative covariance in the constructed hybrid population (where SA alleles are segregating at intermediate frequencies) compared to what is present in either parental population. In addition, one could perform a quantitative trait locus (QTL) analysis on male and female fitness and ask whether the QTL that increases fitness in one sex reduces fitness in the other.

The Evolution of Sex-Biased Genes and Expression

Though we have only a small number of specific examples of segregating sexually antagonistic variants, indirect "-omics" evidence hints at intralocus conflict being widespread. A large amount of data now exists on sex bias in gene expression (SBGE), and there are intriguing evolutionary patterns relating to both coding sequence and regulatory evolution (Parsch and Ellegren 2013; Ingleby et al. 2015; Mank 2017*b*). Some of these sex-biased genes may be involved in interlocus conflict, while others may be subject to intralocus conflict or other processes entirely. Bearing this major caveat in mind, we review the key results. The coding sequence of genes with sex-biased expression (particularly male biased) tends to evolve faster than that of unbiased genes (Ellegren and Parsch 2007; Zhang et al. 2007; Harrison et al. 2015). This pattern is often assumed to be due to rapid adaptive evolution under sexual selection or conflict. However, in genes with sex-limited expression (or very strong bias), selection is absent or very weak in the other sex, possibly making net selection weaker than on unbiased genes (Pröschel et al. 2006; Dapper and Wade 2016). Thus, rapid evolution may be due to relaxed purifying selection rather than adaptive evolution. Consistent with this idea, genes expressed exclusively in the testis harbor more segregating potentially deleterious nonsynonymous and stop-codon SNPs (Gershoni and Pietrokovski 2014). In assessing whether the accelerated divergence of sex-biased genes is due to adaptive evolution, additional analyses have usually found evidence for adaptive evolution when they have been performed (Pröschel et al 2006; Baines et al. 2008; Whittle and Johannesson 2013; Lipinska et al. 2015). In addition, male-biased genes tend to evolve faster than female-biased genes (Ellegren and Parsch 2007; Zhang et al. 2007; Jiang and Machado 2009; Harrison et al. 2015; Ingleby et al. 2015), though there are notable exceptions that suggest this result may depend on the potential for effective sex-role reversal or pleiotropic constraint (Whittle and Johannesson 2013), the degree of phenotypic sexual dimorphism (Lipinska et al. 2015), or the ontogenetic timing at which sex bias is inferred (Mank et al. 2010).

Genes with sex-biased expression also tend to show unusual patterns of regulatory evolution. For example, in multiple species of fly, there is greater expression divergence among populations for male-biased genes than female-biased or unbiased genes (Meiklejohn et al. 2003; Hutter et al. 2008; Zhao et al. 2015; Allen et al. 2017; but see Muller et al. 2011). Moreover, in some species, it appears that, irrespective of sex bias, population divergence in expression occurs more often in males than it does in females, pointing to an asymmetry between sexes in the evolutionary forces that are shaping divergence (Allen et al. 2017). In both fruit flies (Meiklejohn et al. 2003; Zhang et al. 2007) and birds (Harrison et al. 2015), there appears to be high interspecies turnover in which genes are sex biased (i.e., genes that are sex biased in one species may be unbiased in a related species). Moreover, there are numerous genes where the direction of sex bias is reversed across bird species, though few examples of such reversal were reported in flies. In flies, male-biased genes are more likely to be lineage-specific than unbiased genes (i.e., a male-biased gene in one lineage does not exist in a related lineage), though the reverse is true for female-biased genes (Zhang et al. 2007).

Selection on Sex-Biased Genes

Widespread sex-biased gene expression may reflect a history of sexual antagonism, but there has been little effort to directly measure differences in selection on expression between the sexes. This is perhaps unsurprising given that classic methods of phenotypic selection analysis require hundreds of individuals (Lande and Arnold 1983) and that genome-wide expression profiling remains costly on this scale. One notable exception is the work of Innocenti and Morrow (2010), which is unique in attempting to connect SBGE to selection. They sampled 100 haplotypes from a long-term lab population of *Drosophila melanogaster* and assayed the fitness of each haplotype in males and females. They then examined gene expression in 15 of these haplotypes: five lines with medium fitness ranks in both sexes, five lines with high fitness ranks in males but low fitness ranks in females, and five lines with low fitness ranks in males but high fitness ranks in females. They measured how expression in each sex differed with these fitness categories as a proxy for directional selection on expression and found 1,292 genes (7.6%) with a significant sex-by-fitness interaction of the type suggesting sexual antagonism. However, only for 97 of these (0.6%) was there evidence for significant (and opposing) selection in each sex (i.e., strong evidence of antagonism). The larger number could be viewed as an upper limit on the extent of antagonism.

Though the work of Innocenti and Morrow (2010) offers a novel and potentially powerful approach, caution is needed in interpreting the results with respect to the pervasiveness of antagonism and the extent to which it maintains variation.

Consider a hypothetical case where selection favors a larger eye-to-brain ratio in males than is favored in females. If 1,000 genes are differentially expressed between these body parts, then there would appear to be 1,000 genes with sexually antagonistic selection. Are there really 1,000 targets of antagonistic selection or just 1? It is helpful to take the perspective that expression levels are phenotypes and not genes. In studies using traditional phenotypes, one would perform a standard multivariate selection analysis (Lande and Arnold 1983) rather than analyzing each trait separately, as is typical with expression data. While the study of Innocenti and Morrow is currently the best available, the number of haplotypes studied is much smaller than the number of genes analyzed. Correlations among traits reduce dimensionality, a result confirmed through multivariate analyses of the male *Drosophila* transcriptome (Blows et al. 2015). On a practical side, the maximum number of dimensions of variation that can be estimated must be less than the number of independent replicates, regardless of the number of traits measured.

An additional complexity in associating fitness and gene expression is that the relationship between the two may be nonlinear. Early studies of associations between traits and gene expression detected highly nonlinear relationships (e.g., Qu and Xu 2006), which might be expected given the nonlinear relationships of many enzymatic reactions. When studies are designed to detect only directional changes, we may miss aspects of nonlinear selection that could generate sexual antagonism.

Despite these concerns, Innocenti and Morrow's (2010) article remains a hallmark because of its pioneering attempt to link SBGE to fitness. Moreover, several subsequent studies have found intriguing patterns based on the original data. Cheng and Kirkpatrick (2016) found that the fraction of loci identified by Innocenti and Morrow as experiencing sexually antagonistic selection was highest among genes showing intermediate levels of SBGE. This is consistent with the idea that genes with intermediate levels of bias expression are enriched for genes where sexually antagonistic selection in the past resulted in moderate levels of dimorphism but the antagonistic selection is still on-going. In contrast, most unbiased genes are likely unbiased because they are selected for similar expression levels across the sexes, whereas very highly biased genes may have been under antagonistic selection in the past, but the evolution of strong expression dimorphism has resolved the conflict so that current expression variation is no longer antagonistic. In a different study, Hill et al. (2017) obtained sequences from nine of the haplotypes studied by Innocenti and Morrow (2010): five haplotypes with high male fitness and low females fitness and four haplotypes with low male fitness and high female fitness. They identified ~6,000 variants that segregated perfectly between the two fitness classes. Intriguingly, the underlying genes were enriched for those affecting sex-determination and sex-differentiation pathways. Moreover, the underlying genes showed a moderate but significant overlap with the genes Innocenti and Morrow identified as experiencing antagonistic selection on expression. Because the original expression data from Innocenti and Morrow (2010) came from a small number of lines, the potential for false positives is high. The overlap in genes between the two studies suggests that some fraction of the original results consisted of true positives. Yet it remains a challenge to determine how few true positives are needed to drive observed patterns.

In addition to their analysis of the Innocenti and Morrow fly data, Cheng and Kirkpatrick (2016) compared SNP frequency differences between human adult males and females ($N \approx 2{,}000$). Because autosomal SNP frequencies should be the same between the sexes at birth, differences in adults arise from sex differences in mortality effects (or by chance). Parallel to their fly analysis, they observed that intersexual SNP frequency differences (intersexual F_{st}) were greatest for genes with intermediate levels of SBGE, with lower intersexual F_{st} for genes with both low and high levels of expression dimorphism. Though the pattern described by Cheng and Kirkpatrick (2016) is statistically significant, they do not report how much variation it explains. Moreover, and as they discuss, there are other interpretations of this pattern. Nonetheless, the parallel patterns in humans and flies (each using different types of data) could indicate that segregating sexually antagonistic variation is prevalent across the genomes of both species.

The idea of using intersexual F_{st} as a screen for finding genes under sexually antagonistic selection is appealing because it could be applied to many species in nature. However, intersexual F_{st} cannot detect sexual antagonistic selection on reproductive traits and will have low power to detect individual SNPs with sexual antagonistic viability effects because it relies on intersexual differences in SNP frequencies created within a single generation. Nonetheless, the properties of sets of genes with elevated intersexual F_{st} may offer insights into sexual antagonism (Cheng and Kirkpatrick 2016; Lucotte et al. 2016). However, elevated intersexual F_{st} can occur for other reasons, including an intersexual difference in the magnitude of viability selection, even if the direction of selection is the sexually concordant. Because antagonistic selection can cause balancing selection, a more refined list of candidates for sexual antagonism would come from those genes having elevated values of both intersexual F_{st} and Tajima's D, a signature of balancing selection (Mank 2017*a*). We note that the application of the Cheng and Kirkpatrick approach in other systems has shown that, although significant, the variance accounted for by these associations can be quite weak (Wright et al. 2018). We suggest studies should, at the least, attempt to replicate associations in multiple independent samples before drawing strong inferences based on these population genetic approaches. The critical parameters here are gene-specific esti-

mates of intersexual F_{st} between sexes, which, as mentioned above, will likely have a very high sampling variance.

Experimental evolution is an alternative tool for examining sex differences in selection on gene expression. In these studies, replicate populations of a polygamous species are subjected to experimentally manipulated mating systems, which differ in their opportunity for sex-biased selection. Hollis et al. (2014) found that after more than 100 generations of enforced monogamy, *D. melanogaster* gene expression became feminized, with female-biased genes becoming more female biased and male-biased genes less male biased. These results suggest antagonistic selection on sex-biased genes in the base population and that intersexual genetic correlations are relatively strong between sexes. Although promising, we note that a recent study performed in *Drosophila pseudoobscura* using a very similar design failed to replicate this result (Veltsos et al. 2017). Although sex-biased genes were disproportionately influenced by the manipulation, expression was on the whole masculinized rather than feminized.

Resolving Intralocus Conflict

Intralocus conflict may often be transient, being resolved via a variety of mechanisms. All of these solutions involve limiting, or at least biasing, expression of alleles to the sex in which their effects are beneficial. The alignment of expression with selection enables the evolution of dimorphism. These issues have been reviewed in detail by Bonduriansky and Chenoweth (2009), so we will touch only on the major topics and provide additions and updates where appropriate.

One solution to intralocus conflict is sex-specific modifiers of expression. For example, if increased expression is favored in males, then the ideal solution is to have a single allele where expression is elevated in males relative to females, rather than maintaining both high- and low-expression alleles within the population. There is ample evidence of sex-biased expression. If one assumes that this reflects a history of past antagonism, then one expects that sex bias evolved to mitigate conflict. This leads to the prediction of low levels of current antagonism on highly biased genes, consistent with the patterns reported by Cheng and Kirkpatrick (2016). Consider the data from Innocenti and Morrow (2010), who report that 8.5% of biased genes experience antagonistic selection (cf. 7.8% of all genes). If one assumes that all sex-biased genes were historically under antagonistic selection (and if there are no power limits on detecting current selection), then this result indicates that sex bias has resolved antagonism in 91.5% of genes. However, it is impossible to know whether the lack of antagonism among the majority of biased genes reflects the resolution of historical conflict through the evolution of expression bias or whether few of these genes experienced antagonism to begin with.

In a follow-up analysis, Griffin et al. (2013) found that those genes under antagonistic selection tended to have a stronger positive intersexual genetic correlation in expression than genes under other forms of selection (or unselected genes), consistent with the idea that there is a lack of variation to evolve increased sex bias to alleviate antagonism. Furthermore, the strength of the intersexual genetic correlation in expression was a predictor of the magnitude of divergence in sex bias between *Drosophila melanogaster* and related species: those genes with strong intersexual genetic correlations in expression in *D. melanogaster* showed little difference in the degree of sex bias between related species. The latter result suggests that intersexual genetic correlations can constrain evolution over long periods. Multivariate quantitative genetic analyses of genes residing in different *Drosophila* signaling pathways also confirm the importance of between-sex pleiotropic constraints on interspecific divergence (Innocenti and Chenoweth 2013). By contrast, a recent study of sex-biased gene expression in human blood found no association between the extent of sex bias and the strength of the intersexual genetic correlation (Kassam et al. 2016). One possible reason for the discrepancy being that the degree of SBGE in human blood is typically much lower than that seen in analyses of *Drosophila*, which are usually conducted on whole organisms. We note also that although significant negative associations between sex bias and intersexual correlations have been seen in other taxa, there can be an appreciable residual, where quite dimorphic genes can have high correlations. Such a result hints at other pathways to expression dimorphism, such as hormonal regulation (Dean and Mank 2016).

Though expression dimorphism is often assumed to be the outcome of conflict, there are at least two routes by which expression dimorphism can arise that do not involve a history of antagonism. First, even if selection is sexually concordant, expression dimorphism can evolve if mutational effects differ between the sexes. For example, if increased expression is favored in both sexes, a mutation that increases expression in one sex but causes little or no increase in expression in the other sex will be favored and result in expression bias. Second, expression dimorphism could evolve if constraining selection on expression is weak in one sex but strong in the other. Mutations that alter expression in both sexes will be selectively constrained, but mutations that only affect expression in the sex experiencing weak selection may be able to drift to fixation, resulting in expression bias. While it seems likely that antagonism drives much of the evolution of dimorphism (in both expression and phenotypes), it is difficult to exclude the alternatives without additional information. Badly needed are studies of the mutational contributions to SBGE.

Another way to resolve intralocus conflict is for antagonistic alleles to occur preferentially in the sex in which they are favored. In systems with established sex chromosomes, this

could be accomplished by moving conflicted alleles onto or off of the sex chromosome. In chickens, genes inferred to have moved to the *Z* are more likely to be associated with male reproduction than female reproduction (Ellegren 2011). Genes that have been inferred to have moved from the *Z* to an autosome are more likely to be female biased than those moving in the opposite direction. However, there were no such patterns among retrogenes (Toups et al. 2011). In *Drosophila*, there is evidence of gene movement by retroduplication between the X and autosome, with the net rate being higher in the direction of *X* to autosome (Meisel et al. 2009; Metta and Schlotterer 2010). For those genes where the paternal copy is lost, there is little evidence that movement off the *X* changes the direction of a gene's expression bias (Metta and Schlotterer 2010). Further, this set of relocated genes tends to be female biased, counter to intuition based on sexual antagonism. In mammals, there appears to be an excess movement of testis-expressed genes off of the *X* (Emerson et al. 2004), but this may be due to pressure to escape meiotic sex chromosome inactivation rather than related to sexual antagonism. Though many of the studies of gene movement have invoked the notion of sexual antagonism, we are aware of no formal model predictions. Gene relocation often involves a transitory phase involving duplicate copies, and the evolutionary spread of a duplicate in the context of sexual antagonism will likely depend on the fitness consequences of the varying number of copies of alternative alleles in each sex. Thus, a single universal prediction seems unlikely.

Rather than moving onto existing sex chromosomes, sexually antagonistic alleles may be responsible for the evolution of sex chromosomes themselves. Indeed, the major conceptual model for the evolution of sex chromosomes postulates that there will be strong selection for reduced recombination between a gender-determining locus and any linked locus under sexual antagonism to create a strong association between sexually antagonistic alleles and the alleles determining the gender for which the former are beneficial (Fisher 1931; Bull 1983; Rice 1987). For example, the female-beneficial (and male-detrimental) *OB* haplotype in cichlids is tightly linked to a dominant female sex-determination locus (Roberts et al. 2009). What may often begin as a local region of reduced recombination can spread, over evolutionary time, to almost the entire chromosome, as antagonism at other loci outside the initial region are selected to also become more tightly linked to the gender-determining region. Consistent with this idea, Wright et al. (2017) found a greater expansion of the nonrecombining region between the X and Y in guppy populations with low predation where males are more colorful; male color is thought to be Y linked. Van Doorn and Kirkpatrick (2007) argued that sexually antagonistic loci can drive the turnover of sex chromosomes. This can occur, for example, if a new male-determining allele arises near an autosomal sexually antagonistic locus. Such a male-determining allele will come to be in linkage disequilibrium with the male-beneficial allele at the SA locus. If such males are more fit than males carrying the original Y, then the new male-determining allele can spread. This can lead to replacement of the original Y or the maintenance of multiple sex-determining mechanisms within a population. Sex chromosome turnover and multiple sex-determining mechanisms can be found in a variety of frogs, fish, and insects (Bachtrog et al. 2011, 2014).

Whether complete chromosomal recombination suppression evolves following the establishment of a neo–sex chromosome should depend on how abundant antagonistic loci are along the chromosome and whether antagonism can be resolved first via other means before recombination suppression. An interesting case is that of the sex chromosomes in emus (Vicoso et al. 2013). Despite their ancient origin (dating back 120 million years), *Z* and *W* chromosomes are homomorphic, with a large pseudoautosomal region. There is greater sex bias in gene expression on the sex chromosomes compared to the autosome, even in the pseudoautosomal region. This observation has prompted the hypothesis that the evolution of SBGE has sufficiently reduced sexual antagonism to obviate selection for reduced recombination.

Conclusions

Sexual conflict, comprising both inter- and intralocus conflict, can be a powerful force shaping the genome. However, we are some distance from knowing how much of the genome is actively affected by either of these forces. Modern methods of sequencing and analysis allow us to survey the genome and transcriptome with unprecedented detail. However, these approaches alone are limited in their ability to tell us about the mechanisms of selection-driving patterns. We have argued that a central obstacle to this understanding is a mismatch between those traits where we understand selection and those where we understand genetics. In cases of interlocus conflict, where antagonistically interacting phenotypic traits are known, genetic dissection of those traits would allow for an illuminating comparison of rates and patterns of molecular evolution between genes underlying the male and female components of sexually antagonistic selection. Much more attention has been focused on the genetics of intralocus conflict, but here too we usually lack an understanding of selection. For example, there is ample evidence of expression dimorphism, but it is unclear to what extent these biased genes experience sexually antagonistic selection versus other forms of sex-biased selection (e.g., male-male competition). Studies of the phenotypic and fitness effects of rapidly evolving and biased genes are needed. In sum, to convincingly demonstrate the role of sexual conflict in shaping genomic patterns, we will require a greater integration of phenotypic, genetic, and comparative genomic approaches.

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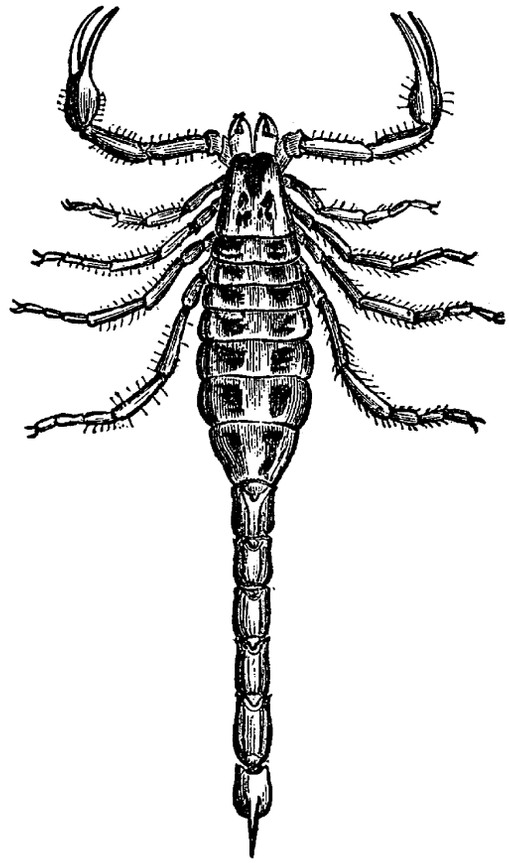

"The species we have is viviparous, carrying its young, eight in number, on its back, until they are three-fourths of an inch in length. When first seen, clinging on the back of the mother scorpion, they are so small that it requires a microscope to examine them satisfactorily. . . . They cling tenaciously, and when by violence they are separated from the mother, she shows manifest signs of distress, running about till she comes in contact with the lost ones, when they immediately climb up and cling again closer than before." From "Scorpion of Texas" by G. Lincecum (*The American Naturalist*, 1867, 1:203–205).