POPULATION GENETICS OF SEXUAL CONFLICT IN THE GENOMIC ERA

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ABSTRACT:

Sexual conflict occurs when selection acts in opposing directions on males and females. Case studies in both vertebrates and invertebrates indicate that sexual conflict maintains genetic diversity through balancing selection, which might explain why many populations show more genetic variation than expected. Recent population genomic approaches based on different measures of balancing selection have suggested that sexual conflict can arise over survival, not just reproductive fitness as previously thought. A fuller understanding of sexual conflict will provide insight into its contribution to adaptive evolution and will reveal the constraints it might impose on populations.

In many sexually reproducing species, divergent reproductive interests can arise between the sexes over courtship, fertilization and offspring investment, and these conflicting interests can lead to substantially different optimal phenotypes in males and females [1-3]. In such cases, selection will act in opposing directions on the sexes, a situation referred to as sexual conflict or sexual antagonism. Sexual conflict over a given phenotypic trait can occur through the interaction of alleles at two or more loci (inter-locus sexual conflict)[4-6] . This form of sexual conflict has been somewhat difficult to study using molecular population genetic methods, as it lacks a clear evolutionary signature in DNA sequence. As a result, the majority of recent population genomic studies have focused on cases where there are genetic trade-offs for male and female fitness from alleles at a single locus (intra-locus sexual conflict). This situation arises when male and female phenotypes are underpinned by the same genetic architecture[7]. With the exception of sex-specific Y and W chromosomes, males and females within a species share the vast majority of their genome, which creates a high potential for intra-locus conflict when male and female reproductive interests are not aligned through strict monogamy. Indeed, classic work measuring reproductive fitness in *Drosophila*[8] has suggested that intra-locus sexual conflict occurs at many different loci throughout the genome. Intra-locus sexual conflict can be ultimately resolved via alleles or expression patterns that are sex-specific in their effects[9-13].

The persistence of sexual conflict, and the mechanism by which it occurs, have important implications for the nature and magnitude of genetic diversity within populations[14-19]. Positive selection and purifying selection deplete populations of genetic variation over time. Nevertheless, many populations display more genetic diversity for traits under strong selection than expected, possibly because of balancing selection generated by intra-locus sexual conflict[15,20]. Intra-locus sexual conflict produces balancing selection by selecting for or against different alleles at a specific locus depending on whether they are present in females or males. The resulting genetic diversity—and by implication sexual conflict—shapes the adaptive potential[21,22] of populations and their resilience to extinction[23,24].

The democratization of genome sequencing has revitalized the topic of sexual conflict and, in some cases, has made it possible to identify sexually antagonistic alleles. The ready availability of large volumes of genomic data also makes it possible to empirically test long-standing theories in both model and non-model organisms. In some cases, data from

genomic studies have challenged traditional ideas about sexual conflict. For example, previous evidence suggested that sexual conflict is primarily the result of an allele increasing the reproductive fitness of one sex at some cost to the other[14-16]. However, more recent studies point to the potential for sexual conflict over viability or survival, where an allele increases the likelihood that one sex will live long enough to reproduce at some cost to the other[17,18,25]. Published[25-28] and preliminary[29] studies have also sparked new debate, for example, about how often and how quickly sexual conflict can be resolved.

Here, I review how recent genomic studies are contributing to, and sometimes re-shaping, our understanding of sexual conflict. I start with recent case studies that have identified sexually antagonistic loci that illustrate the role of sexual conflict in generating balancing selection. Then, I describe emerging population genomic approaches for the study of sexual conflict and discuss what they can reveal about the causes of sexual conflict and about the varying potential for sexual conflict across different regions of the genome. Finally, I comment on the potential for sexual conflict to aid or hamper adaptation, and identify important outstanding questions regarding the nature and persistence of sexual conflict within populations.

Identifying the locus of sexual conflict

In order to understand the types of genes that are subject to sexual conflict, it is important to identify loci with sexually antagonistic alleles. Candidate gene approaches, transcriptome analysis and genome-wide association studies (GWAS) have been applied to a number of animals to identify specific loci of large conflicting effect on male and female reproductive fitness[14, 16,17]. The case studies discussed below illustrate the relationship between sexual conflict and balancing selection, but also reveal interesting caveats. Of note, sexual conflict in these cases seems to arise primarily over reproductive success, as alleles that increase the reproductive output of one sex reduce the relative number of offspring when expressed in the other.

Sexual conflict maintains genetic diversity.

In *Drosophila melanogaster*, studies comparing the transcriptomes of pesticide-resistant and pesticide-susceptible flies identified alleles at the cytochrome P450 locus *Cyp6g1* that

confer resistance to DDT and other common insecticides[30,31]. In the presence of DDT, the resistance allele dominates. However, studies of reproductive fitness have shown that in some genetic backgrounds and in the absence of insecticide, these resistance alleles have sexually antagonistic effects on reproductive success. In this case, the resistance alleles are associated with increased fecundity and shorter larval development times in females, and reduced mating success[30,31] and reproductive investment[16] in males (Fig. 1a). Sexual conflict has led to a clear indication of balancing selection whereby both the resistance alleles (which are selected for in females) and susceptibility the alleles (which are selected for in males)[16] are maintained, illustrating how balancing selection between females and males can retain polymorphisms within populations.

Another example of balancing selection involves the arginine vasopressin receptor 1a (*Avpr1a*) and oxytocin receptor (*Oxtr*) loci. These genes have important roles in reproductive behaviour in mammals[32-34] and are therefore candidates for studies of sexual conflict. In bank voles (*Myodes glareolus*), microsatellite alleles in the regulatory regions of these loci are associated with different reproductive success rates, presumably because the microsatellites alter gene expression levels. For both loci, the effects are opposite in males and females, with alleles associated with greater numbers of newborns for fathers also correlated with fewer weaned offspring for mothers[20]. Like the DDT resistance alleles in *Drosophila*, sexually antagonistic selection acting on these behavioural loci leads to balancing selection, which maintains allelic polymorphism.

Not all balancing selection on reproductive genes is due to sexual conflict.

It is worth noting that genetic signals of balancing selection on loci with reproductive effects are not always due to sexual conflict. For example, GWAS in Soay sheep (*Ovis aries*) implicated an allele at the relaxin-like receptor 2 (*Rxpf2*) locus in male horn size variation, which also correlates with variation in male reproductive success[17]. Interestingly, this locus exhibits signatures of increased genetic variation that might be expected from sexual conflict. However, in this case, the increased genetic variation is not because of a cost to females, which experience no fitness effect of the allele, but rather because there is a survival cost to males carrying the large-horn allele, resulting in an advantage for heterozygotes (Fig. 1b). This heterozygote advantage in turn generates balancing selection to maintain both alleles in the population.

Partial resolution of sexual conflict does not reduce diversity.

The frequent occurrence of phenotypic dimorphism[1,9] (such as differences in size, morphology or behaviour) and genomic dimorphism (such as differential gene expression[10], splicing[11,12], methylation[13] and even dominance reversal[14]) indicates that when sexual conflict is sufficiently strong, the shared genome can evolve to be expressed in a sex-specific manner (Box 1). This dimorphism permits male and female phenotypic averages to diverge and approach their sex-specific fitness optima, at least partially resolving antagonistic selection. However, balancing selection can persist even when sexual conflict has been partially resolved.

For female Atlantic salmon (*Salmo salar*), reproductive success and size are positively correlated[35]. These fish grow indeterminately, which results in a reproductive advantage for females that mature later because, on average, they will be larger than early-maturing females. The association between size and reproductive success is less pronounced in males, and they tend to mature earlier, most likely to minimize the risk of pre-spawning mortality[36]. GWAS has shown that nearly 40% of the variation for size at maturity in both sexes is associated with alleles at the vestigial-like family member 3 (*Vgll3*) locus[14]. The shared genetic architecture of this trait presents substantial opportunity for sexual conflict. However, in this example, sexual conflict has been partially resolved by dominance reversal, whereby the allele that confers late maturity is dominant in females but recessive in males (Fig 1c). Although the underlying mechanisms are unknown, this locus is presumably associated with increased reproductive fitness in females but is costly to males, and the reversal of dominance maximizes the number of females expressing the phenotype while at the same time minimizing the number of males suffering from it[14]. In this way, both alleles are maintained because of the net fitness advantage of heterozygotes, but conflict has been mitigated.

Population genomics of sexual conflict

Although we have learned a great deal about sexual conflict from the single-locus examples above, these examples are of loci with large fitness effects and it is not clear if they are representative of sexual antagonism more generally. Indeed , classical assumptions about

sexual conflict[8] predict many sexually antagonist loci with alleles of small effect distributed throughout the genome. These subtle-effect alleles have proved more difficult to pinpoint using quantitative genetic approaches, possibly because of the limitations of mapping highly polygenic traits in outbred populations owing to the Beavis effect[37]. Without methods to better identify many smaller-effect loci, it is not clear how pervasive sexual conflict is within the genome.

Recently, population genomic approaches have proved useful in scanning for putative signatures of sexual conflict based on DNA sequence diversity parameters[38], the idea being that balancing selection from sexual conflict will lead to distinct signatures in molecular sequence data. These approaches are based on sequence data alone and, unlike the case studies described above, do not require information about phenotypes or fitness. Different studies have adopted different measures of balancing selection, each of which provides distinct insights into the nature of sexual conflict. However, it is important to note that these measures can be inaccurate for any particular locus for reasons described below, and therefore cannot be used to identify specific antagonistic loci. Nevertheless, these tools can be effective for evaluating the potential for sexual conflict when used to compare different regions of the genome or different types of genes [39].

Measuring balancing selection from sequence diversity.

Preliminary[29] and published studies[25,38,40,41] of sexual conflict have measured nucleotide diversity with Tajima's D (Box 2), which estimates the proportion of nucleotide sites in a given sequence that are polymorphic within a population. This approach is based on the assumption that balancing selection from sexual conflict will lead to the maintenance of multiple alleles, which will in turn cause higher than expected levels of sequence diversity compared to regions not under balancing selection. Provisional data generated using this method suggests that a substantial proportion of the genome is subject to sexual conflict[29] which may exert a constraint on the evolution of sexual dimorphism. Published studies show that putative sexually antagonistic loci are distributed non-randomly across different genomic regions[40,41], which is discussed further below.

This technique gives little insight into the source of sexual conflict, as nucleotide diversity alone cannot distinguish sexual conflict over reproductive fitness from conflict over viability or survival (Fig. 2). Moreover, other factors that are independent of sexual conflict can lead

to elevated nucleotide diversity, including heterozygote advantage[42,43] (such as at the *Rxpf2* in Soay sheep[17]) and selection related to fluctuating ecological pressures (such as alternative food sources[44]). Thus, Tajima's D can identify sites within the genome that are under putative balancing selection, but it cannot distinguish sexual conflict loci from loci subject to other causes of balancing selection.

Measuring balancing selection from inter-sexual genetic differentiation.

Measures of genetic differentiation, or differences in allele frequency, are often applied to compare populations or even closely related species. However, two recent studies have used one such measure, the fixation index (F_{ST}), to assess the extent of allelic differentiation between males and females in a population[18,25] . Importantly, allele frequency is identical between the sexes at conception before selection acts because it is defined at the start of each generation by Hardy-Weinberg equilibrium based on the allele frequency of the parental population. . In other words, newly conceived male and female zygotes will have the same allele frequencies, and F_{ST} between them will be non-significant. Theoretically, any differences between allele frequencies observed in adults are therefore the result of sexual conflict over viability or survival rather than over reproductive fitness. The focus on sex differences in viability or survival is somewhat counter to the case studies in the preceding section which show that sexual conflict primarily arises over reproductive output[14,16,19], and this might be in part because of an investigation bias toward reproductive traits.

Both of the studies indicate that there are many loci throughout the human genome with significant sexually antagonistic effects on survival or mortality[18,25]. This conclusion suggests that the mortality load from sexual conflict may be very high, although it is not known where in the life cycle this selection gradient occurs as only adults have been studied. It is worth noting that if genetic differentiation between females and males is the product of sexual conflict over adult survival or mortality (for example, from differential predation) the age of the samples could have an important influence on F_{ST} estimates. However, if sexual conflict occurs over viability and embryonic lethality, it is sufficient to sample individuals that have survived until birth (or eclosion in the case of insects).

Sex-biased genes are typically thought to represent largely resolved sexual conflict over optimal expression (Box 2)[10,26,45], however one study[25] found that moderately sex-biased genes showed elevated F_{ST} in humans. This observation suggests that loci with intermediate

levels of sex-biased expression might in fact contain substantial unresolved conflict. However, inter-sexual genetic differentiation alone cannot distinguish loci subject to sexual conflict over survival from loci where sexual conflict has been resolved through the evolution of separate genetic architecture[46-48](Fig. 2). When sexual conflict has been resolved, alleles affecting viability or survival in one sex will have little or no effect in the other (Fig. 3). Such loci are under positive or purifying selection in one sex but experience the mutational input from both, which will lead to more genetic diversity than expected [49-51]. Consistent with this notion, recent work suggests that differences in allele frequency between males and females in humans are indeed a result of sex-specific survival[52].

Estimates of inter-sexual genetic differentiation are influenced by sex-differences in dispersal[53] and hemizygosity on the sex chromosomes (Box 3), and these phenomena may therefore generate false signatures of sexual conflict. It is also worth noting that sexual conflict has the potential to generate high inter-sexual genetic differentiation estimates for any given locus in specific situations. For example, high selection coefficients acting on dominant variation would result in surviving males and females having completely different alleles, and therefore $F_{ST} = 1$. By contrast, the maximum potential estimate of genetic differentiation for loci with sex-specific genetic architecture will be lower than for sexually antagonistic loci, because alleles will be selected for only in one sex and a mix of alleles will be present in the other sex (Fig. 3). Estimates in humans[18,25] have revealed low levels of inter-sexual differentiation across a broad array of loci, consistent with either sex-specific selection or low selection coefficients from sexual conflict.

Combination approaches.

By using multiple population genomic measures obtained from the same population data, it is possible to differentiate between some of the causes of sexual conflict and to gain a clearer understanding of the patterns of diversity that are observed (Fig 2). In particular, combining measures of genetic variation (Tajima's D) with estimates of inter-sexual genetic differentiation (F_{ST}) can be used to differentiate between alternative scenarios regarding the nature of sexual conflict, and determine whether it more often originates from differences in reproductive fitness or from differences in mortality (Fig. 2). For example, sexual conflict over viability or survival leads to high F_{ST} and high Tajima's D . However, although sex-differences in dispersal[53]and hemizygous exposure of recessive lethal variation on the X or Z

chromosome also lead to high $F_{ST,}$ they do not cause elevated Tajima's D. Similarly, sex-specific viability or survival resulting from sex-specific genetic architecture, where an allele at a locus may influence the survival of one sex but have no influence on the other, will also increase genetic differentiation between males and females but Tajima's D will not increase. Thus, although both Tajima's D and F_{ST} have been used separately as proxies for sexual conflict[25], they are most informative when combined. However males and females must be sequenced separately in order to compare allele frequencies and estimate inter-sexual differentiation. Preliminary studies using this combined approach indicate that elevated F_{ST} is more often the result of sex-specific genetic architecture rather than ongoing sexual conflict over viability or survival[54], However, it will be helpful to see results from a broad array of taxa.

The genomic distribution of conflict

The case studies of sexual conflict loci in *Drosophila*[16,30,31], voles[19] and salmon[14] (described above) are all autosomal genes, which are inherited equally between males and females. However, regions with asymmetrical inheritance between the sexes—such as organelle genomes and the sex chromosomes—are predicted to accumulate sexually antagonistic alleles more rapidly than autosomal regions because they are more often selected in one sex than the other[55]. These regions are therefore particularly interesting for studying the dynamics and signatures of sexual conflict. This is not to say that the autosomes are unlikely to accrue sexually antagonistic variation, as clearly they do. Rather, the proportion of antagonistic variation might be greater for regions with asymmetrical inheritance than would be expected based on the fraction of the genome that they contain.

Extra-nuclear genomes.

Organelle genomes have the potential to accumulate sexually antagonistic genetic variation, which is not as easily resolved through acquiring sex-specific genetic architecture as for the nuclear genome[56]. In most species, mitochondrial genomes are passed from the mother to both her sons and daughters, as are chloroplast genomes in many plant species. This pattern of maternal inheritance pattern creates the potential for these organelle genomes to accumulate mutations that harm males, even if they confer no benefit to females. This

situation is referred to as The Mother's Curse[57] and it occurs because transmission rates are influenced only by mutations that influence female fitness and are therefore unaffected by male-specific mutations.

Organelle genomes are completely physically linked and, because they never recombine, it can be technically challenging to identify which specific region or gene within these genomes affects male fitness. Instead, most animal studies to date have used lengthy backcrossing schemes to introgress different mitochondrial genomes across multiple genetic backgrounds, and then compare male reproductive fitness or other related parameters[58-59]. Using this approach, some mitochondrial genomes in animals have been shown to have deleterious effects on male sperm quality and reproductive rate [58-61], consistent with predictions that maternally inherited organelle genomes can remain in the population even if they harm male reproductive fitness. Male-harming mitochondrial genomes still segregate in the population either because they confer some advantage to females or because they do not incur a cost.

Although challenging, it is possible in some systems to identify the specific mutations in organelle genomes that affect male fitness. Recent work in *Drososphila melanogaster*[61] showed that a mutation that reduced expression of the mitochondrially-encoded enzyme cytochrome oxidase II impairs male sperm development. Similar effects are observed for mutations in organelle genomes of dioecious plants that produce in cytoplasmic male sterility by preventing pollen development [62,63]. Although it is theoretically possible for cytoplasmic male sterility to be caused by maternally inherited mutations in either the mitochondrial or chloroplast genome, most known cases have been shown to be mitochondrial in origin [62]. For example, in rice (*Oryza sativa*), cytoplasmic male sterility has been shown to result from a duplication of the mitochondrial *atp6* locus[64], a mutation that does not affect female fertility. Interestingly, in some cases of cytoplasmic male sterility pollen development can be restored through compensatory nuclear mutations[62,64]. For example, duplication of a nuclear pentatricopeptide repeat gene silences the *atp6* duplication in rice[64]. This observation suggests that when selection in males is sufficiently strong it can act on nuclear-encoded genes that interact with the mitochondrial genome to reinstate male fertility[62].

Feedback loops on sex chromosomes.

Sex chromosomes are the product of recombination suppression between the X and Y (or Z and W) chromosomes[65], and there is increasing evidence that this process occurs in order to resolve sexual conflict[27,66-68]. Data from studies in guppies (*Poecilia reticulata*)[27] and sticklebacks[66] are consistent with the theoretical prediction that recombination between the X and Y chromosomes is selected against in order to maintain male-benefit alleles on the Y chromosome[69-72], thereby limiting their inheritance to males. In effect, male-specific genetic architecture is created through inheritance[27,66] of the Y chromosome, and sexual conflict is resolved because these alleles are simply never present in females. This process is not limited to male heterogametic species, as a similar effect has been shown in a female heterogametic cichlid, in which the formation of the W chromosome resolved sexual conflict over color[68].

Once recombination is arrested between the X-chromosome and the Y-chromosome, sex chromosomes show asymmetrical inheritance, and the X chromosome spends more time in females and the Y chromosome is limited to males. This asymmetry means that sex-linked loci are more often selected for their effects in one sex than the other. As a result of this unbalanced selection in males and females, these chromosomes are predicted in some cases to accumulate sexually antagonistic variation more rapidly than regions with equal inheritance [72-74]. This process has been observed in many sex chromosome systems, and has been extensively reviewed[73,75,76].

The pseudo-autosomal region (PAR) is on average equally inherited between males and females. Recombination can occur at any point on the PAR and, for species with a relatively large PAR compared to the non-recombining sex chromosome region, recombination will rarely occur right at the PAR-sex chromosome boundary. Thus, regions near the PAR boundary, but still occasionally recombining, are more often inherited by one sex than the other along with the sex chromosome that they are linked to. In effect, these regions are partially-X or partially-Y linked. Partial sex-linkage is predicted to lead to more sexually antagonistic alleles[72,77,78] than expected for autosomal regions, but fewer than expected for fully sex-linked regions. Consistent with this prediction, population genetic approaches have shown that there is evidence of increased variation (Tajima's D) for genes on the PAR of *Silene latifolia*, a dioecious plant[40,41], which is presumably the result of balancing selection

from sexual conflict. Preliminary data from studies of guppies is consistent with the *Silene* results[54], suggesting this pattern might be a widespread.

Sex chromosomes form to resolve sexual conflict, and therefore also present two interesting positive feedback loops. After recombination is halted between the X and Y chromosomes, the partial sex-linkage in the PAR creates a positive feedback loop where the increased rate of accumulation of sexually antagonistic variation will lead to selection to further expand the non-recombining region to resolve the resulting conflict. A different positive feedback loop also acts across the whole of the X and Y chromosomes after recombination ceases, causing them to accumulate even more sexually antagonistic variation at a faster rate than the autosomes. Both of these positive feedback loops act in concert to make sex chromosomes a hotspot of sexual conflict within the genome.

Conclusions and future perspectives

Our best examples of sexual conflict loci[14,16,19] clearly show that sexual conflict leads to balancing selection and, in these cases, the primary source of sexual conflict is reproductive fitness. However, population genomic approaches provide evidence that sexual conflict could also arise over viability or survival[18,25]. Population genomic approaches also reveal that different regions of the genome, particularly those with uneven inheritance between the sexes, accumulate sexually antagonistic variation more rapidly than other regions[59,65,73]. Despite these advances, many issues remain unresolved.

Untangling the causes of sexual conflict.

Population genomic methods have recently proved useful in identifying potential sexual conflict within the genome. Because sexual conflict results in balancing selection[16,19], it is possible to use the molecular signature of balancing selection to scan genomes as a proxy for sexual conflict. However, molecular genetic signatures of balancing selection can result from a host of other factors. Thus, it remains unclear how much of the detected balancing selection is a result of sexual conflict and it is not yet known how pervasive sexual conflict is within the genome.

Other population genomic approaches are based on inter-sexual differentiation and recent studies using this technique raise the possibility that sexual conflict can arise over viability

and survival[18,25], as well as reproductive fitness[15,16,19]. However, it is unclear if these patterns are the result of sexual conflict or sex-specific genetic architecture[52], and the answer has important implications regarding the amount of unresolved conflict present in populations. Indeed, combination approaches using multiple population genomic parameters will be required to distinguish between alternative sexual conflict scenarios, and they will also provide answers about the nature and transience of sexual conflict.

Clarifying the role of sexual conflict in evolution.

Given the role that sexual conflict plays in maintaining genetic diversity, it has at least the potential to aid in adaptation, which is of particular interest given recent human-induced shifts in climate and other environmental conditions, often referred to as the Anthropocene[79-81]. However, it remains unclear whether lineages with higher levels of sexual conflict, which likely arise from mating systems, exhibit greater than average levels of diversity across the genome. Settling this issue will require a more detailed understanding of the proportion of the genome affected by sexual conflict and balancing selection, and of the speed at which conflict is resolved and balancing selection relaxed. It also remains unclear whether the diversity arising from sexual conflict increases evolvability. Some evidence suggests that conflict aids adaptation[22,24], however there is also counter evidence suggesting that conflict impedes adaptation[21,23,82], and it is therefore unclear whether unresolved conflict hinders adaptation more than it helps. The rapid ecological changes of the anthropocene provide a natural laboratory to test the adaptive role of conflict, and will help determine whether sexual conflict should be considered as an indicator of extinction risk.

Solving these outstanding questions will require the effective integration of multiple population genomic methods with phenotypic studies of reproductive fitness and ecological adaptation.

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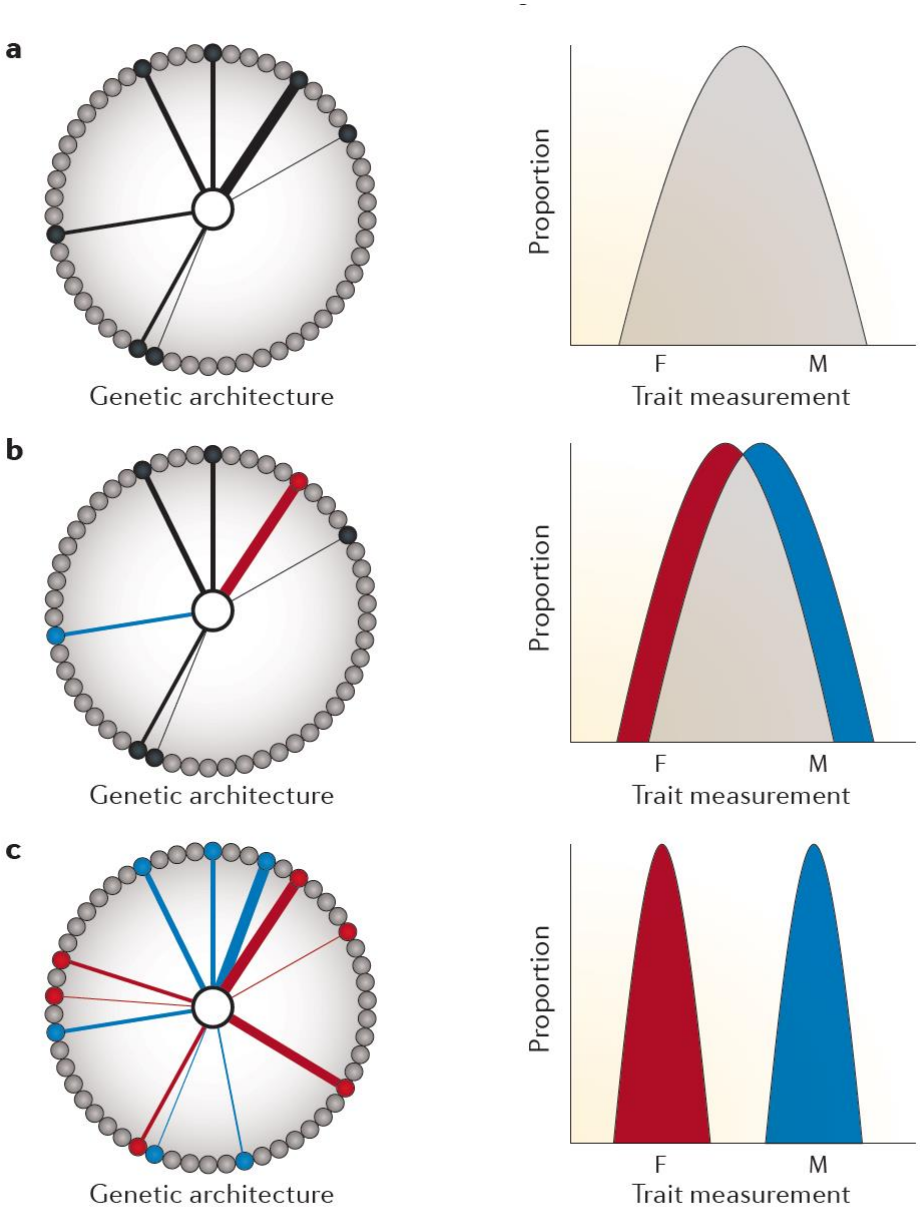
Box 1 Resolving sexual conflict with sex-specific genetic architecture.

Intra-locus sexual conflict is the result of selection acting in divergent directions on male and female phenotypes that are underpinned by a shared genetic architecture[7]. However, both forward[46] and reverse[47,48,83,84] genetic studies have indicated that the genetic architecture underlying many traits expressed in both sexes can differ substantially between females and males. In theory, sex-specific genetic architecture, where an allele affects one sex but not the other, resolves contradictory selection pressures[45,46] and relaxes balancing selection.

Sex-specific architecture for genes present in both sexes can occur via different routes. Mutations in genes predominantly expressed in one sex tend to have sex-specific phenotypic effects[85], suggesting sex-biased gene expression may be important in the construction of sex-specific genetic architecture[17]. However, this is not the only mechanism, as alleles expressed in both sexes can also have different phenotypic effects in females and males, or even affect only one sex[46,86]. Other potential mechanisms[7] include sex-specific splice variants[87,88], and even sex-reversal in the dominance of specific alleles[14].

Although we do not yet have a complete understanding of how genetic architecture evolves from shared to sex-specific, it is not difficult to envision the general progression. In the figure below, circles represent all the loci that could contribute to variation in a given phenotype that is expressed in both sexes. Lines represent loci that do contribute to variation in the phenotype (genetic architecture), and the width of the line corresponds to the size of the effect. In Panel A, female (F) and male (M) phenotypic optima differ substantially for a trait with shared genetic architecture (black lines), and male (blue) and female (red) distributions of this trait are largely overlapping. In theory, balancing selection from sexual conflict can be quite high for these loci. Over time (Panel B), loci emerge with sex-specific effects (male-specific effects indicated by blue lines, female-specific effects indicated by red lines), partially resolving conflict and allowing for initial divergence of the trait between females (red) and males (blue). Balancing selection will be maintained for shared genetic architecture, but will be reduced for loci with sex-specific effects. In some cases (Panel C.), the genetic architecture may become completely separate between the sexes and the distribution of the trait completely non-overlapping. There will be no

evidence of balancing selection resulting from sexual conflict for these loci, as sexual antagonism will have been resolved.



Box 2. Tajima's D and Balancing Selection

Although other methods to study balancing selection from sequence data exist based on common haplotypes[89] or polymorphism[90], most studies have employed Tajima's D, a measure of nucleotide diversity developed by Fumio Tajima[91] that is used extensively in population genetic analysis. Specifically, Tajima's D measures the difference between the average number of sites that differ between any two individuals (pairwise diversity), and the total number of sites that are variable, or segregating, in a population. Pairwise diversity can be estimated based on population size and mutation rate, and Tajima's D in effect measures the deviation from this expected diversity.

The purpose of Tajima's D is to test whether stretches of DNA are evolving neutrally, which is expected to result in roughly equal estimates of pairwise diversity and number of segregating sites. As a result, Tajima's D ≈ 0 under neutrality. When Tajima's D deviates from neutrality, the value can be used to distinguish different models of selection. Negative values for Tajima's D indicate less polymorphism is observed than expected, consistent with purifying selection or a recent selective sweep in the region, both of which deplete genetic variation. Positive values indicate there is greater observed polymorphism than expected, which can result from balancing selection to maintain multiple variants in a population. It is important to note that these predictions apply only for old polymorphisms that have been segregating in the population for many generations as newer mutations tend to show slightly less variation than expected[92].

It is also important to remember that Tajima's D can be influenced by population size as well as recent demographic factors, such as population expansions or contractions[93,94]. These factors complicate comparisons across related populations or species. However, these factors are less of a concern in genomic scans within populations that compare different types of genes. Tajima's D is also influenced by mutation rate, which can be a complicating factor in intra-genomic scans because mutation rate can vary across different genomic regions [95].

Finally, Tajima's D is a conservative measure, and failure to detect significant estimates for any one locus does not provide conclusive evidence against balancing selection. For this reason, it is most useful to compare the distribution of Tajima's D for different sets of genes to determine whether certain regions or functionalities are more often associated with balancing selection than a comparison group of genes[26, 38,40].

Box 3 Complications of sex chromosome hemizygosity.

Estimates of inter-sexual genetic differentiation, such as F_{ST}, on the sex chromosomes can be confounded by hemizygosity, which can create a false signal of elevated sexual conflict on sex chromosomes where it is also theoretically expected[72,76]. Recessive variation that is lethal to both sexes will be more often selected against in the heterogametic sex (males in XY species, females in ZW species), which possesses only one functional copy of X- or Z-linked loci. Haemophilia is an example of a recessive X-linked trait in humans that is associated with a significant increase in mortality in affected individuals[96]. All males with the disease-causing allele express the trait because they are hemizygous and lack a second copy of the locus, and they will therefore experience higher mortality selection. Selection against the allele in females only occurs in homozygotes, which are much less frequent than hemizygous males. Female heterozygotes do not typically express the trait and therefore do not suffer increased mortality. The frequency of the haemophilia allele is therefore lower in males than females after mortality selection because of male hemizygosity, even though haemophilia is detrimental in both sexes and therefore not sexually antagonistic. Hence, it is difficult to determine whether elevated levels of inter-sexual genetic differentiation on the sex chromosomes are the product of selection resulting from hemizygosity or from sexual conflict. However, the value of Tajima's D would not be affected by this phenomenon because it would not lead to increased balancing selection.

Fig 1. Case studies of balancing selection and sexual conflict. In each case, high fitness genotypes are in green, low fitness in blue . A. The DDT resistance allele at the Cytochrome P450 6g1 (*Cyp6g1*) locus shows sexually antagonistic effects on *Drosophila* male and female fitness in the absence of DDT in some genetic backgrounds[16,30,31]. At this point, the fitness effects of the resistance allele are not yet known in heterozygotes, and for simplicity, hypothetical dominant effects are shown. B. The Relaxin-like receptor 2 (*Rxpf2*) locus affects horn size in Soay sheep. Larger horns in males are associated with greater reproductive success but a simultaneous survival cost, resulting in male heterozygote advantag[17]. As female fitness is unaffected, balancing selection is not a result of sexual conflict C. Dominance reversal for the vestigial-like family member 3 (*Vgll3*) locus partially resolves sexual conflict over size at maturation in salmon[14]. The allele for late maturation (L) is dominant in females and recessive in males. The allele for early (E) maturation is dominant in males and recessive in females. Dominance reversal affects which phenotype is expressed by each sex and the effect is clearly seen in heterozygotes, which have identical genotypes at this locus but express different phenotypes to achieve optimal sex-specific fitness.
Panel b is adapted with permission from references 17 and 97.

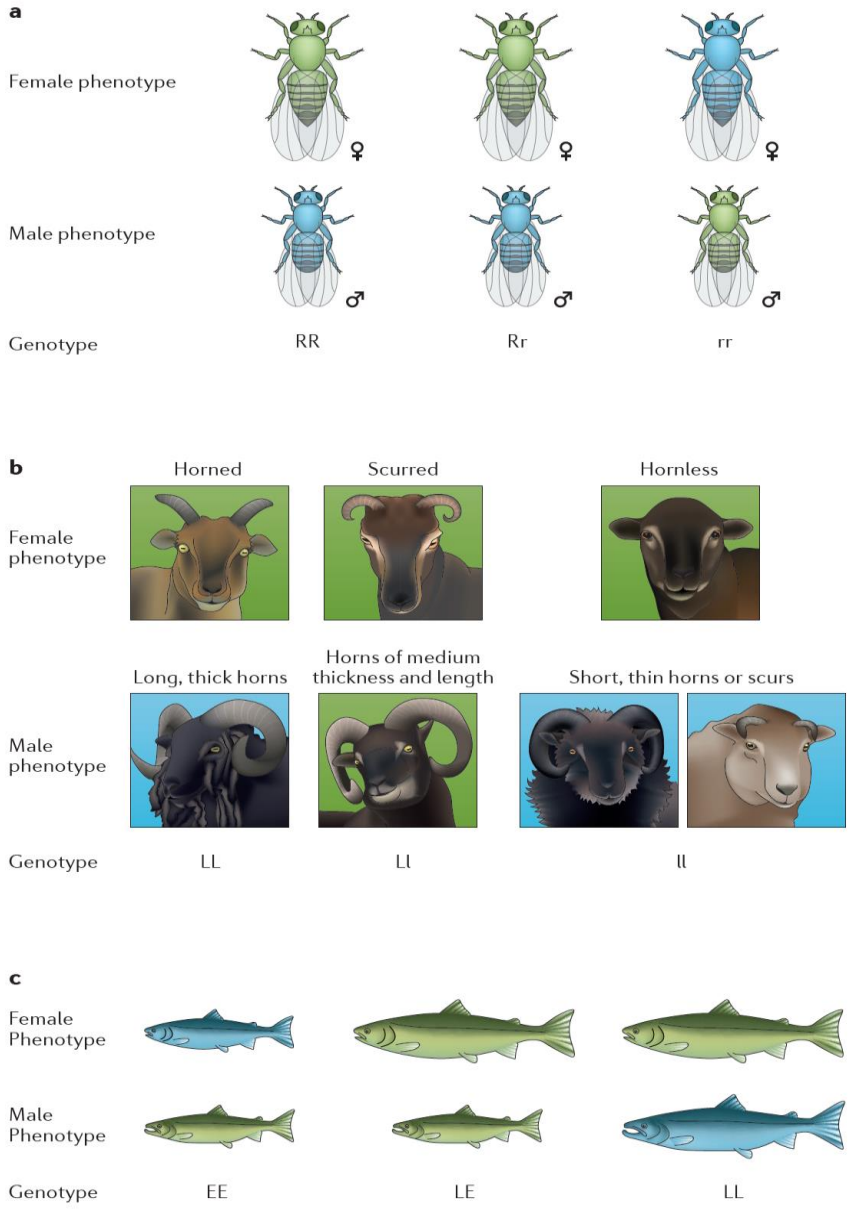


Fig. 2. Population genomics measures of sexual conflict. Tajima's D, a measure of the proportion of variable sites, and F_{ST}, a measure of genetic differentiation between males and females for loci present in both sexes, have both been used separately as measures of sexual conflict[18,25,29,40].However, these measures can be used together to differentiate between alternative sexual conflict scenarios. For example, sexual conflict over reproductive fitness will result in elevated Tajima's D, but will not produce significant F_{ST}. By contrast, conflict over survival will produce both elevated F_{ST} and Tajima's D. Importantly, factors other than sexual conflict can also produce significant F_{ST} and Tajima's D. Factors related to sexual conflict are depicted in red, all others are depicted in black.

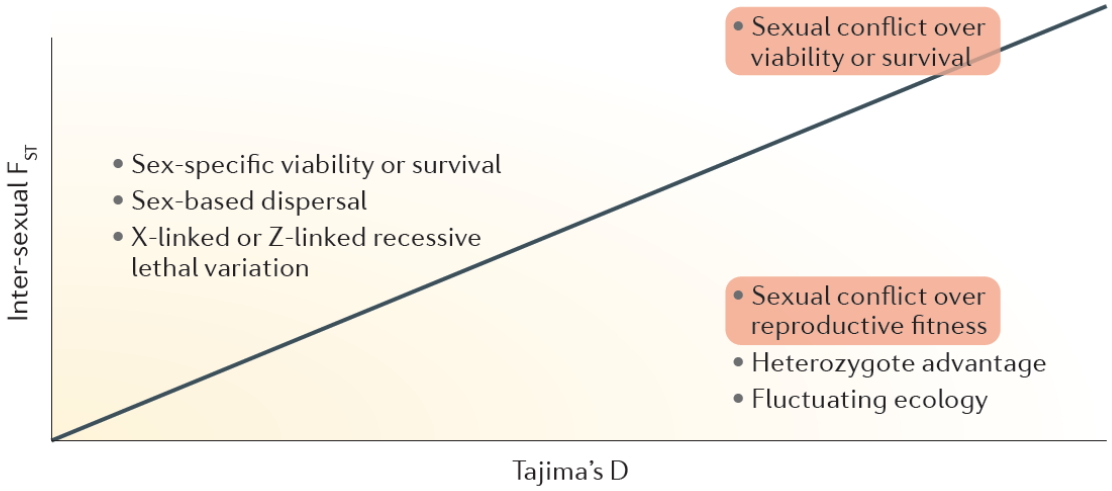
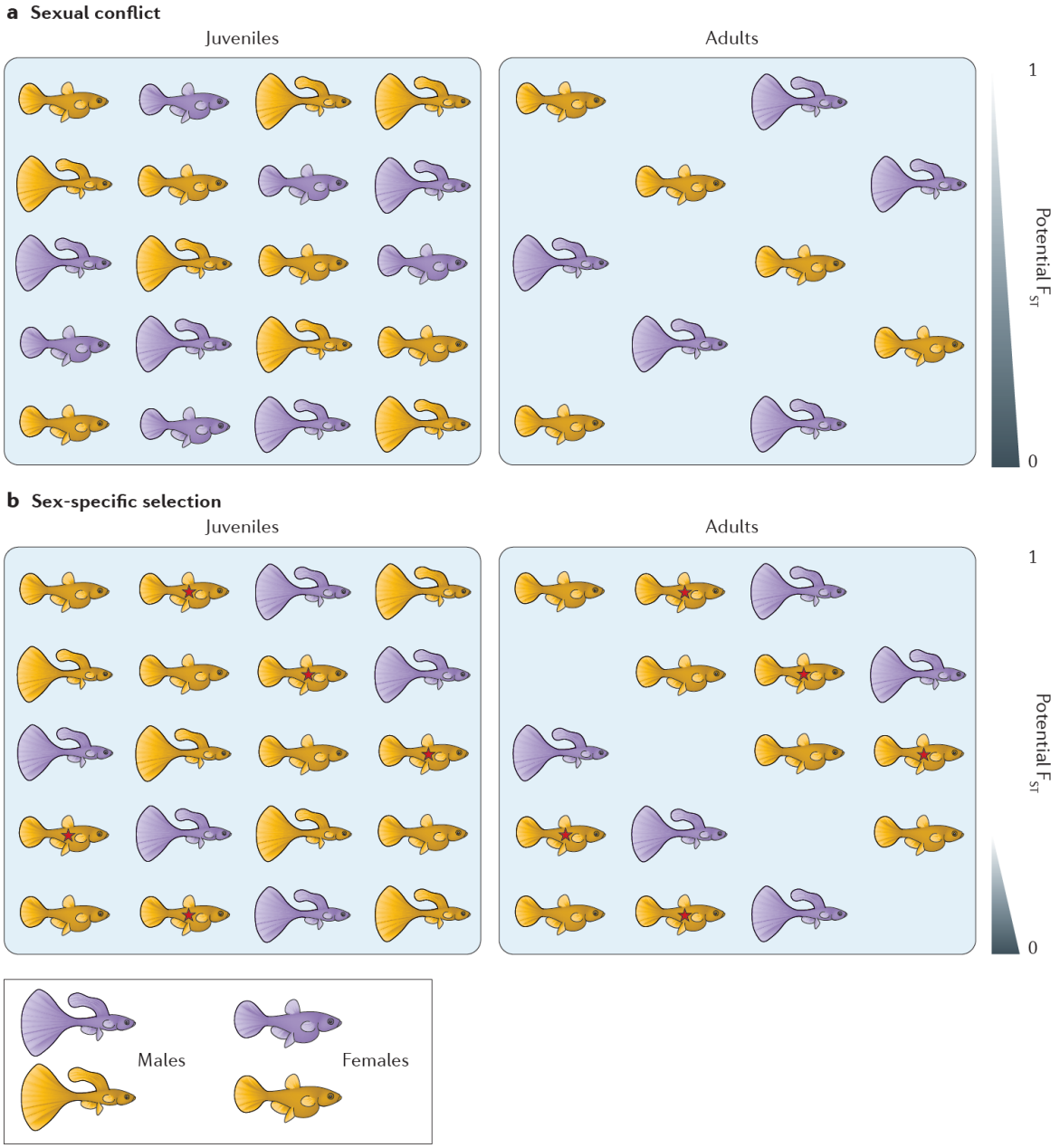


Fig. 3. Differential effects of sexual conflict and sex-specific selection on F_{ST} for a two-allele locus. A. Sexual conflict over survival would occur in a population where only green females and black males survive to adulthood and both alleles are expressed in both sexes. F_{ST} depends on the strength of selection in each sex, and can theoretically reach 1 if alternative alleles perfectly assort between males and females after selection. B. Sex-specific selection over survival occurs when the black allele is only expressed in males (owing to sex-specific genetic architecture); although females carry the allele, they do not express it (denoted with *) and it is not selected against in females. The maximum potential F_{ST} is less than that under sexual conflict as, although surviving males all possess the black allele, females contain both alleles.



Glossary

BALANCING SELECTION –the evolutionary process whereby more alleles are maintained in a population than would be expected from the mutation rate and population size. It results from fluctuating selection (that is, the direction of selection) over time, space or, in this case, sex.

BEAVIS EFFECT: A phenomenon in quantitative genetic studies in which the effect sizes of significant QTL are overestimated, and the effect size of non-significant QTL are underestimated. Because significance is related to sample size, the Beavis effect implies that identifying small but significant effects on fitness will require very large samples often not feasible in lab or natural populations.

CANDIDATE GENE – a pre-specified gene of interest based on its known function.

DOMINANCE REVERSAL –a change in the dominance – recessivity relationship of an allele between different groups, in this case between males and females.

FIXATION INDEX (F_{ST}) –a measure of differences in allele frequency between two groups , typically owing to genetic structure. In the context of comparing males and females from a single population, F_{ST} can result from differences in survival or viability.

GENETIC ARCHITECTURE –the underlying genetic basis of a phenotypic trait and, in particular, the genetic basis for phenotypic variation in the trait.

GENOME-WIDE ASSOCIATION STUDIES (GWAS) – studies based on a statistical method to determine what regions of the genome are associated with a trait of interest.

HARDY-WEINBERG EQUILIBRIUM – a fundamental principle of population genetics which predicts that allele and genotype frequencies at a given locus will remain constant in a population in the absence of other evolutionary influences.

HETEROZYGOTE ADVANTAGE –, occurs when the presence of two different alleles at a given locus confers increased reproductive fitness compared to either homozygote. Also referred to as heterosis or overdominance.

HEMIZYGOUS –the state of having only one copy of a chromosome in an otherwise diploid organism. Hemizygosity occurs most frequently on the sex chromosomes, where the heterogametic sex only has one functional copy of X- or Z-linked loci.

INTER-LOCUS SEXUAL CONFLICT- the result of evolutionary antagonistic interactions between males and females for alleles at two or more loci. In this form of sexual conflict, adaptation at one locus that favours one sex at some cost to the other is followed by counter-adaptations at a different locus for the harmed sex. The cycle of adaptation and counter-adaptation can repeat many times, resulting in an arms race between males and females

INTRA-LOCUS SEXUAL CONFLICT –the result of conflicting selection pressures for males and females over alleles at a single locus. In this form of sexual conflict, alleles at a single locus have opposing effects on male and female fitness.

MICROSATELLITE – a short nucleotide repeat at a particular region of a chromosome. Microsatellites often have many alleles of different repeat number within a population.

MORTALITY LOAD –the proportion of individuals in a cohort that die prior to reproduction.

POSITIVE SELECTION – selection to increase the frequency of a new advantageous mutation within a population.

PSEUDO-AUTOSOMAL REGION – the portion of the sex chromosome that still recombines in the heterogametic sex and is not inherited in a strictly sex-linked manner.

PURIFYING SELECTION – removal of deleterious variation from a population by selection.

REPRODUCTIVE FITNESS- the reproductive success, such as the number of viable offspring, of a given genotype. It is typically measured by the average contribution of the genotype to the next generation of the population compared to other genotypes.

SELECTIVE SWEEP – the reduction or elimination of genetic variation near a beneficial allele that has recently been fixed in a population due to strong positive selection. Sweeps are the result of genetic linkage between the beneficial mutation and nearby variation.

SEX-BIASED GENES – genes that are expressed more in one sex than the other.

TAJIMA'S D- a measure of the proportion of polymorphic sites within a given locus, or of the percentage of segregating sites.

TRANSCRIPTOME ANALYSIS- a technique where the RNA levels are compared between treatment and control groups for all coding genes in the genome.

VIABILITY –the proportion of embryos with a given genotype that survive development.

ONLINE ONLY

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Key Points:

- Case studies on several loci with sexually antagonistic alleles, identified by genetic and genomic approaches, reveal that sexual conflict leads to balancing selection to maintain both female-benefit and male-benefit alleles.
- The signature of balancing selection from population genetic data is increasingly useful in assessing the amount and distribution of sexual conflict within the genome.

- The causes of sexual conflict remain unclear and, different population genetic tools must be combined to determine whether sexual conflict results primarily from reproductive success or survival.
- Sexual conflict can be resolved through a variety of mechanisms. However, balancing selection is only relaxed when sexual conflict is fully resolved.

ToC blurb

Sexual conflict is thought to increase population genetic diversity though balancing selection, which has important evolutionary implications. This Review discusses how population genomic approaches are contributing to a deeper understanding of sexual conflict and how it is resolved.