Huxley Review 2020

Selfish genes and sexual selection: the impact of genomic parasites on host reproduction

Nina Wedell
Bioscience, University of Exeter, Penryn Campus, Penryn TR10 9FE, UK
N.Wedell@exeter.ac.uk

Running title: Selfish genes and sexual selection

Abstract

Selfish genetic elements (SGEs) such as replicating mobile elements, segregation distorters, and maternally inherited endosymbionts, bias their transmission success relative to the rest of the genome to increase in representation in subsequent generations. As such they generate conflict with the rest of the genome. Such intra-genomic conflict is also a hallmark of sexually antagonistic (SA) alleles, which are shared genes between the sexes but that have opposing fitness effects when expressed in males and females. However, while both SGEs and SA alleles are recognised as common and potent sources of genomic conflict, the realisation that SGEs can also generate sexually antagonistic selection and contribute to sexual conflict in addition to generate sexual selection is largely overlooked. Here I show that SGEs frequently generate sex-specific selection and outline how SGEs that are associated with compromised male fertility can shape female mating patterns, play a key role in the dynamics of sex determination systems, and likely be an important source of sexually antagonistic genetic variation. Given the prevalence of SGEs their contribution to sexual conflict is likely to be greatly overlooked.

1. What are Selfish Genetic Elements?

Selfish genetic elements (SGEs) are ubiquitous in eukaryotes and prokaryotes (Burt & Trivers, 2006; Lindholm *et al.,* 2016). As the name implies, these are genes that do not play fair but manipulate the rest of the genome in a variety of ways to enjoy a transmission advantage to subsequent generations and therefore increase in frequency. As such they are an important source generating intra-genomic conflict (conflict between different agents within the genome due to biased transmission) in addition to the potential negative impact on gene function of their activity (e.g. increasing/ decreasing gene expression or immobilising genes by translocation/ insertion/ deletions, Table 1). Furthermore, their mode of generating transmission bias can have substantial fitness costs to the host. SGEs frequently target gametogenesis and reproduction to ensure enhanced transmission. There are many different types of SGE that affect the genome in a variety of ways. The different characteristics can be distilled into two types: an over-replication advantage (e.g. mobile genetic elements in genomes) and a transmission distortion advantage (e.g. meiotic drivers in populations), but they all violate the rule of equal inheritance (Table1).

The most common type of SGE are transposable elements (TEs). TEs increase in frequency by encoding for enzymes that catalyse their copy number within the genome. They are frequent in eukaryotes and prokaryotes and can make up a large part of the genome (e.g. ~45% of the human genome derive from transposable elements (Lander *et al.,* 2001)). Another group of SGE are segregation distorters that include driving chromosomes (meiotic drive), which if associated with the sex chromosomes cause sex ratio distortion (Jaenike, 2001). They also include maternally inherited endosymbionts that kill or feminize males as they cannot transmit the endosymbiont, with resources instead diverted to the female function (Werren, 1997). Meiotic drivers are common in insects, mammals and plants (Lindholm *et al.,* 2016). Endosymbionts are also ubiquitous (e.g. mitochondria), and bacterial endosymbionts that affect host reproduction by inducing reproductive incompatibility are very common in arthropods (Zeh & Zeh, 1996). There is also a growing recognition that the microbiome of animals shapes many aspects of organismal fitness, but also has the potential to act selfishly, for example by competing over nutrients in the gut at a cost to its host (Bell *et al.,* 2019).

There are several consequences stemming from the intragenomic conflict and direct impact on gene function generated by SGEs. They are a potent force in shaping the structure and function of the genome, can increase the mutation rate, affect the evolution of genes, genomes, cells, gene regulation and gene expression (e.g. Jurica & Stoddard, 1999). In addition, they play a role in the formation of sex chromosomes and sex chromosome turnover, influence effective population size, viability and gene flow and may even aid speciation (Werren, 2011). They can also have dramatic impact on behaviour of individuals, including sexual behaviour (Wedell, 2019). In this review I outline how SGEs can shape sexual selection by affecting mate choice and mating strategies, but also generate sex specific selection, frequently resulting in sexual conflict and sexually antagonistic selection.

2. How can SGEs affect sexual selection?

Seeing that SGEs are ubiquitous and affect most aspects of organismal life it is perhaps not surprising that they also influence sexual selection and sexual conflict. There are several reasons why this is to be expected: individuals should avoid mating with partners carrying

genes associated with costs, and many SGEs target sperm production affecting male fertility. Below I outline how these aspects of sexual selection are affected by SGEs.

a) SGEs affect mate preferences

We might expect individuals that carry SGEs to be discriminated against during mate choice as they carry genes that result in reduced fertility, reduced offspring production, or offspring of reduced fitness or attractiveness. However, there are remarkably few examples demonstrating that SGEs make their carriers less attractive. There has to be a cue revealing that individuals carry a SGE. Unless there is a change in behaviour, odour or morphology of SGE carriers, it is not clear how individuals could discriminate against them. So, are there cues revealing SGEs? With regards to behavioural changes, unless an individual carrying the SGE suffers a direct cost (i.e. pathogenic effect), it is not always clear whether behavioural changes are to be expected (Wedell, 2019). In insects infected by the endosymbiont *Wolbachia* there is evidence that the bacteria can directly invade brain regions and interfere with the nervous system and affect mate preferences of infected individuals (Strunov *et al.,* 2017). In *Drosophila melanogaster* the *w*Mel strain is found throughout the insect brain (Albertson *et al.,* 2013). *Wolbachia* has been shown to influence mate preferences in some studies (e.g. Arburthnott *et al.,* 2016), whereas other studies have found no effect (e.g. Champion de Crespigny & Wedell, 2007). It is currently not clear if these different findings indicate that *Wolbachia* has a differential impact depending on the host genotype, or are due to other factors not controlled for. In contrast, in the fly *D. paulistorum* the strain *w*Pau is confined to regions in the fly brain that processes olfactory and auditory information (Strunov *et al.,* 2017). *D. paulistorum* is a species complex where different strains of *Wolbachia* cause reproductive incompatibilities between infected and uninfected flies. Remarkably, mate preferences are dependent on the specific strain of *Wolbachia* hosts carry with females preferring to mate with males carrying the same *Wolbachia* strain as their own, ensuring compatible pairings (Miller *et al.,* 2010; Schneider *et al.,* 2019). It is currently not clear what impact *Wolbachia* in the brain has in terms of shaping insect mate preferences. One possibility is that endosymbionts and other SGEs have the potential to modify odour cues used in mate recognition and mate choice by uninfected individuals. For example, *Wolbachia* reduce mate discrimination in *Nasonia* jewel wasps (Chafee, 2011), and in the terrestrial isopod *Armadillium vulgare*, feminizing *Wolbachia* affects mate attraction by altering female cuticular odour cues (Richard, 2017). There is now a growing realisation that endosymbionts, as well as gut microbiota and other bacteria, can directly affect cuticular hydrocarbons, sex pheromone production, and other odour cues used in mate choice (e.g. Engl & Kaltenpoth, 2018).

With non-bacterial SGEs there is more limited evidence of mate preference. For example, in *D. pseudoobscura* harbouring a sex-ratio distorting meiotic driver (SR), females do not discriminate against males despite large fitness cost (Price *et al.,* 2012). By mating with SR-carrying males, females will produce the more common sex (daughters) and may also suffer reduced fertility as SR males transfer smaller ejaculates (Price *et al.,* 2008*a, b*). In *Teleopsis dalmanni* stalk-eyed flies carrying a sex ratio distorter (an X-linked meiotic driver), females prefer to mate with males with long eye-stalks. This signals that they carry a genetic suppressor of sex-ratio drive meaning females will sire both sons and daughters (Cotton *et al.,* 2014). On the other hand, in mice carrying an autosomal meiotic driver, the *t*-complex, heterozygous females avoid mating with males carrying the *t*-haplotype. This may be advantageous because homozygous recessives are lethal (Lenington, 1991). Again odour cues are involved, with the *t*-complex being contained in an inversion system that also harbours the MHC alleles used in kin recognition (Lindholm *et al.,* 2013). However, mate choice is not

always present and it is suggested that *t*-specific female preferences may not be evolutionarily stable (Sutter & Lindholm, 2016).

In summary, there is only limited evidence for mate discrimination against carriers of SGEs. For the cases where this has been documented, mate choice appears to be based on cues that are directly linked to the SGE – usually odour cues, although eye-stalk length appears to be a reliable signal of males carrying a genetic suppressor of sex ratio drive in stalk-eyed flies. So why is there such scant evidence of SGEs-based mate choice? One reason may be a lack of genetic linkage between the SGE and the preference allele due to recombination (Nicholls & Butlin, 1998; Lande & Wilkinson, 1999). It is interesting to note, that in the stalk-eyed flies there is evidence of a tight linkage between the preference alleles and sex ratio drive (Johns *et al.,* 2005). A recent theoretical model also shows that preference can only persist in the presence of a cue that reliably indicates a male's distorter genotype (Manser *et al.,* 2017). We may therefore predict that selfish endosymbionts are more likely to have an effect on mate choice than other SGEs, as there is scope for these bacteria to have a direct impact on both odour production and invading the central nervous system of their host where cue processing takes place.

b) SGEs affect male fertility and sperm competition

In contrast to the somewhat limited evidence of SGEs shaping mate preferences, there is ample evidence to show that SGE-carriers frequently suffer reduced gamete production (Zanders & Unckless, 2019). Males in particular that carry different types of SGE have reduced sperm production (Price & Wedell, 2008). While female gamete- killers operate by exploiting the asymmetric meiosis in females, where one meiotic product is selected to become the gamete (Chmatal *et al.,* 2014), they are less commonly observed than SGEs that target sperm. This may be because female drive can result in population extinction (Hamilton, 1967), and to a greater impact of gamete reduction on female compared to male fitness. There are two main ways SGEs target male spermatogenesis to increase their transmission success. Segregation distorters do this by eliminating allelic rivals during meiosis by selectively killing sperm that do not carry the distorter. Meiotic drivers achieve their transmission advantage by being the only sperm type remaining in drive-carrying males' ejaculate (Courret *et al.,* 2019). Post-segregation distorters such as maternally inherited endosymbionts achieve their transmission advantage by killing or feminizing males, or by modifying sperm function resulting in zygote death when eggs lacking the endosymbiont are fertilized. This resulting reproductive incompatibility (cytoplasmic incompatibility, CI) means that uninfected females have dramatically reduced offspring production, whereas infected females who are compatible with both infected and non-infected males' sperm produce offspring that carry the endosymbiont. This differential offspring production translates into a large transmission advantage favouring the spread of the endosymbiont through a population (Werren, 1997). However, sperm modification by post-segregation distorters, and sperm immobilisation and killing by segregation distorters, result in reduced sperm production and therefore may result in transfer of less sperm to females at mating compared to non-carrying males. There are exceptions to this rule, for example male *T. dalmanni* carrying sex ratio drive (SR) do not suffer reduced sperm production, but instead produce and deliver as many sperm as wild-type males. It is suggested that males have evolved to compensate for sperm loss due to SR by increased sperm production to match wild type male ejaculate production (Meade *et al.,* 2019). Whether this is due to lower overall sperm production and delivery by *T. dalmanni* males per mating compared to other fly species and/or due to unknown trade-offs with other fitness related traits, is currently not clear (Meade *et al.,* 2020).

The magnitude of the sperm killing/modification of SGE-carrying males can be substantial. The reduction in male fertility ranges from no significant impact on sperm numbers (e.g. *T. dalmanni* mentioned above) to a reduction of more than 50% as has been shown in several species carrying sex-ratio drive (Price & Wedell, 2008). In addition, the mechanism whereby the gametes are rendered inviable can have deleterious impacts on the surviving SGE-carrying sperm (Price & Wedell, 2008). For example, in *D. pseudoobscura* SR males only produce X-linked sperm as all the Y-sperm are killed. However, the act of sperm killing appears to have a spill-over effect reducing the vigour of the surviving sperm that carry SR (Price *et al.,* 2008*a*). It is also possible that female behaviour post mating affects the number of sperm delivered by SGE-carrying males thereby reducing the likelihood of fertilization (i.e. cryptic female choice (Eberhard, 1996)). This requires that the cost of mating is relatively low allowing polyandrous females to discriminate against specific males post-mating. In many animals, females eject sperm following insemination. For example, female feral fowl eject the ejaculate after being inseminated by a subordinate male (Pizzari & Birkhead, 2000), and sperm ejection is common in many other birds, mammals, and insects (e.g. Snook & Hosken, 2004). It is currently not known if females preferentially eject sperm following mating with males carrying SGEs. In *D. simulans,* sperm are preferentially lost from the females' sperm storage following mating to males carrying sex-ratio drive (SR). However, it is not known if the removal of SR males' sperm is due to a specific response by females to sperm carrying the SR driver, or is a response to receiving small overall ejaculates (Angelard *et al.,* 2008). There is little previous evidence that females can detect meiotic drivers in sperm, and it therefore seems likely that *D. simulans* females respond to the significantly smaller ejaculates transferred by SR males (Price *et al.,* 2009). Whether female sperm dumping is a general strategy to guard against ejaculates carrying SGEs is not known, and is predicted to occur only when the cost of mating to females is low.

Even if females are unable to detect the ejaculate of SGE-carrying males and preferentially eject sperm following insemination, there are additional strategies that they can adopt to reduce the risk of fertilizing their eggs with SGE carrying males' sperm. As SGEs frequently compromise males' sperm production, this often translates into reduced sperm competitive ability (Price & Wedell, 2008). This is because the outcome of sperm competition is often dependent on relative sperm number (Parker, 1970). In addition, the method of sperm killing/modification by SGEs often results in reduced performance in sperm competition over and above the impact of reduced sperm numbers (e.g. Price *et al.,* 2008*a*). This critically sets up a link between males carrying SGEs and poor sperm competitive ability, which in theory should favour polyandry (female multiple mating) as a strategy to promote sperm competition and reduce the risk of fertilizing their eggs with SGE-carrying males' sperm (Zeh & Zeh, 1996). Again, the cost of polyandry has to be relatively low. In support of this prediction, female *D. pseudoobscura* evolving in the presence of males carrying a sex ratio distorter (SR) rapidly evolved increased mating frequency and rate of remating (Price *et al.,* 2008*b*). Subsequent work has shown that polyandry is a very effective strategy that undermines the transmission advantage of SR (Price *et al.,* 2010). Female mating patterns are influenced by the presence of SGEs that reduce male fertility also in house mice and flies (Lindholm *et al.,* 2016). This indicates the presence of SGEs may in general promote polyandry as a female strategy to reduce the risk of producing offspring sired by SGE-carrying males, and as a consequence also limit the spread of the SGE.

In summary, there is ample evidence that SGEs have a detrimental impact on the reproductive success of SGE-carrying males by compromising their fertility. Reduced male

fertility can affect female mating decisions, often by promoting polyandry and sperm competition as a strategy to reduce the risk of siring their offspring by SGE-carrying males.

3. SGEs affect sex determination

SGEs have been shown to play a key role in the evolution and turnover of sex chromosomes (Kozielska *et al.,* 2010; Mank *et al.,* 2014). Selfish sex chromosomes cause sex ratio bias (Table 1) that in turn can result in population extinction (Hamilton, 1967; Price *et al.,* 2010), or suppression (Jaenike, 2001). Sex ratio distorters either promote genetic suppression or evolution of new sex determination systems as a way to restore sex ratio to unity. The cost of drive and the strength of selection associated with sex ratio distortion is suggested to affect the outcome, with strong drive favouring a change in the sex determination system, whereas weak drive favours accumulation of suppressors (Lyttle, 1981; Kozielska *et al.,* 2010). Selfish endosymbionts can cause feminization of genetic males, and microbe-induced parthenogenesis regularly occurs in arthropods (Kageyama *et al.,* 2012). It is also suggested that TEs through their influence on the expression of sexual development genes, often with pronounced sex-specific effect, can influence sex determination including sex chromosome evolution (Dechaud *et al.,* 2019). Hence a variety of SGEs have a major influence on the evolutionary dynamics of sex chromosomes.

SGEs, sex chromosome evolution and sex chromosome turnover

SGEs that cause sex ratio distortion (Table 1) often target sex determination mechanisms including the sex chromosomes themselves (Ma *et al.,* 2014; Courret *et al.,* 2019). As such sex chromosomes are vulnerable to the invasion of segregation distorters. This may not be surprising seeing that any gene on the X/Z can efficiently drive against the Y/W (and *vice versa*) resulting in sex ratio distortion (Hamilton, 1967). This in turn will promote strong selection to restore sex ratio to unity, which can favour the evolution of new sex chromosomes or new ways to determine sex. For example, segregation distorters have promoted the evolution of new mechanisms of sex-determination in rodents (e.g. wood-lemmings, moles and voles), as well as in flies (including the house fly), and scale insects (Beukeboom & Perrin, 2014). A recent model has even suggested that meiotic drive can give rise to sex chromosomes because any new sex determining allele will be favoured when linked to a sex-specific meiotic driver and therefore rapidly spread as a new sex chromosome (Úbeda *et al.,* 2015). In support of this prediction is the recent finding that in a population of the African monarch butterfly *Danaus chrysippus* harbouring male-killing *Spiroplasma* endosymbionts, a neo-W sex chromosome has hitchhiked to high frequency as the male killer has spread through the population. There appears to be a perfect genealogical congruence between the genome of the male-killing *Spiroplasma* and the neo-W sex chromosome (Martin *et al.,* 2020), suggesting that male-killing has favoured the rise of this new sex chromosome. In general sex-chromosome turnover frequently appears to involve autosome-sex chromosome fusion resulting in neo-sex chromosomes in vertebrates (e.g. Kitano & Peichel, 2012), and invertebrates (e.g. Carabel Paladio *et al.,* 2019) and are associated with faster evolution of post-zygotic isolation and diversification (Turelli & Begun, 1997; Lima, 2014). In turn neo-sex chromosomes often involve small and repeat-rich chromosomes (e.g. Ahola *et al.,* 2014), suggesting a role for SGEs such as TEs.

Sex determination and differentiation of arthropods can also be perturbed by endosymbionts and promote evolution of new sex chromosomes. For example, some populations of *A. vulgare* pill bugs harbour feminizing *Wolbachia* that turn ZZ males into females (Leclercq *et*

al., 2016). As a consequence, the effective population size of the W chromosome is reduced eventually resulting in its elimination (Rigaud, 1997). As a consequence of *Wolbachia*-induced feminization, all individuals are females but ZZ genetic males; those inheriting *Wolbachia* develop as females, whereas uninfected embryos develop as males, meaning there has been a transition from genetic to endosymbiont-determined sex determination. In addition, a new female determining factor that converts genetic males into females has recently been discovered. Females from these lines are thought to be ZZ genetic males converted into females by an unknown feminizing agent termed the "*f* element". Further work has shown that this genetic element has triggered the evolution of a new W sex chromosome by horizontal transfer of part of the bacterial genome into the pillbug's nuclear genome (Leclercq *et al.,* 2016). This complicated scenario in *A. vulgare* suggests that *Wolbachia* promoted sex chromosome turnover by first causing the loss of the W sex chromosome, and then by inserting a new sex-determining region into the nuclear genome. This sequence of events suggests that the birth of the new sex chromosome in the pill bug has its origin in the horizontal gene transfer of an initially feminizing endosymbiont (Leclercq *et al.,* 2016). Evidence of the wide-spread ongoing tension between SGE-fuelled sex determination and mechanisms to restore sex-ratio to unity, is the frequent occurrence of a variety of aberrations such as gynandromorphs, in addition to sex-specific lethality (e.g. male killing) and conversion of gender (e.g. feminization of genetic males). Such sexual abnormalities can be caused by selfish maternally transmitted endosymbionts such as *Wolbachia, Rickettsia, Arsenophonus, Spiroplasma* and *Cardinium* bacteria, and by microsporidian protists (Kageyama *et al.,* 2012) that interfere with the sex-determining systems (Ma *et al.,* 2014).

Segregation distorters also have the potential to fuel the turnover of sex chromosomes by invasion and initiating silencing mechanisms to suppress their action (Meiklejohn & Tao, 2009). Silencing of sex-linked genes is a common occurrence and involves meiotic sex chromosome inactivation (MSCI), and other inactivation mechanisms such as RNA interference and methylation (Bird, 2019; Vogel *et al.,* 2019). The co-evolution of SGEs and their silencing mechanisms on the sex chromosome can lead to reproductive incompatibilities between populations harbouring different segregation distorters and suppressors and may even contribute to speciation (Meiklejohn & Tao, 2009). Furthermore, in addition to the reduced recombination of sex chromosomes, these silencing mechanisms can promote new sex determination systems that allow SGEs to escape inactivation and sex chromosome degeneration. For example, it is suggested that gene silencing of the Y chromosome in the fly *D. albomicans* may have initiated the process of degeneration (Zhou & Bachtrog, 2012). In addition, new sex-determining mechanisms such as novel sex chromosomes can facilitate a selective sweep of the sex determining region that may also result in hitchhiking of linked genes with large fitness effects (Hall, 2004; Nolte *et al.,* 2013, Miyata *et al.,* 2017). This means there is the potential that SGEs can also increase in spread by being tightly linked to high-fitness alleles under positive selection (Mank *et al.,* 2014).

In summary, selfish sex chromosomes and maternally inherited endosymbionts that cause sex ratio distortion can favour new ways of determining sex to restore sex ratio to unity. This can involve a variety of mechanisms and we are only now beginning to unravel the complex interaction between SGEs and novel ways to determine sex.

4. SGEs can generate sexual conflict and sexually antagonistic selection

SGEs enjoy a selfish transmission advantage with many showing asymmetrical transmission either through males (e.g. sperm killers), or females (e.g. selfish endosymbionts). While there are some SGEs that are exclusively transmitted in males (e.g. paternal sex ratio in *Nasonia* wasps (Werren, 1991)), many SGEs predominately show a sex-biased transmission in females. For example, mitochondria and other cytoplasmically transmitted agents are (almost) exclusively inherited from mother to offspring (Werren, 1997). Female gametes are usually substantially larger than sperm, in part due to a larger volume of cytoplasm that can harbour selfish endosymbionts that are hitchhiking to the next generation. It is even suggested that one reason that sperm are generally small (over and above the numerical superiority favoured by sperm competition (Parker, 1970)) is because they carry little cytoplasm, which reduces the risk of passing on hitchhiking SGEs to offspring (Randerson & Hurst, 1999). Because of the asymmetrical sexual inheritance of some SGEs, this can translate to differential selection imposed on males and females.

For SGEs that are equally transmitted through both sexes, the overall cost to the individual carrying the SGEs will shape the transmission success. In some cases, the outcome is a less effective transmission of the SGE if greater transmission is associated with considerable fitness costs to the host. For endosymbionts and females this conflict is less apparent and may even be non-existing as their respective fitnesses are often aligned. For example, in the fly *D. simulans*, the Riverside strain of *Wolbachia* has gone from imposing a 15-20% fecundity cost to providing a 10% fecundity benefit to females in less than 20 years of coevolution (Weeks *et al.,* 2007). Moreover, many SGEs while not causing sex ratio distortion, also have sex-specific effects. For example, many TEs show pronounced sex-specific activity (Dechaud *et al.,* 2019). The differential expression of SGEs in males and females has the potential to generate sexual conflict through their potentially sexually antagonistic effect. This is because males and females share most of their genome and develop many of the same traits, but each sex frequently has different optimal trait values, creating intra-locus sexual conflict (Bonduriansky & Chenoweth, 2009). This means that SGEs have the potential to fuel such intra-locus sexual conflict by their sex-specific effects (Wedell, 2013; Mank *et al.,* 2014). Below I outline a few examples to illustrate how different SGEs can generate sexual conflict.

a) Endosymbionts promote female fitness through feminizing selection

Endosymbionts are almost exclusively maternally inherited and therefore the evolutionary interests of the endosymbiont and female function are often aligned, which frequently translate into feminizing selection to promote female fitness. An extreme example is the situation in the wasp *Asobara tabida*, where female ovary development is entirely dependent on *Wolbachia* infection – if females are cured of *Wolbachia* they become sterile (Dedeine *et al.,* 2001). In general, we predict that maternally inherited endosymbionts such as *Wolbachia* in arthropods and mitochondria in animals would enhance female fecundity as this increases their own transmission success and hence the evolutionary interests of females and endosymbionts are frequently aligned. In support of this suggestion, in lab-adapted *D. melanogaster* females, *Wolbachia* increases insulin/IGF-like signalling (IIS) resulting in increased fecundity (Tomoatsu *et al.,* 2009). Endosymbiont-enhancing female fitness is also predicted to increase the longer the duration for coevolution, a prediction supported by empirical findings (e.g. Weeks *et al.,* 2007). However, due to the fact that males and females share a genome, genes that are shaped by feminizing selection to maximize female fitness can result in reduced male fitness when expressed in males. For example, in *D. simulans,* the Riverside strain of *Wolbachia* is associated with increased female fecundity (Weeks *et al.,* 2007), whereas in males *Wolbachia* reduces sperm production (Snook *et al.,* 2000), and sperm competitive success (Champion de Crespigny & Wedell, 2006). *Wolbachia* therefore

generate strong sex-specific fitness differences. Similarly, endosymbionts that cause feminization of genetic males will clearly impose a cost on the male function. For example, feminization of males has the potential to have a detrimental impact on sexually selected traits expressed in males such as odour and visual cues used in mate choice. While there is to date no definitive evidence that feminizers have a detrimental effect on male reproductive success by affecting the expression of sexually selected traits, this is a real possibility. In many feminized systems, some males tend to escape feminization and there are naturally occurring curing agents such as exposure to high temperature and antimicrobial products that remove the endosymbiont resulting in the resurgence of males (Werren, 1997), allowing this prediction to be tested.

A negative intersexual genetic correlation for fitness is frequently interpreted as evidence for the existence of widespread intra-locus sexual conflict where a high male fitness genotype gives rise to a low fitness female and *vice versa*. However, this negative intersexual correlation may instead be due to endosymbionts causing reproductive incompatibilities between infected males and uninfected females (Duffy *et al.,* 2019). For example, *Wolbachia* (and other endosymbionts) frequently cause reproductive failure in crosses between infected males and uninfected females (CI). *Wolbachia* will therefore reduce the fitness of uninfected females mated to infected males, while uninfected males will not suffer this fitness reduction if they mate with infected females. In fact, uninfected males often have higher fitness than infected males that can have compromised sperm production and sperm competitive ability (e.g. Champion de Crespigny & Wedell, 2006). This asymmetry in fitness between the sexes can generate a strong negative intersexual genetic correlation for fitness, thus mimicking intra-locus sexual conflict. In support of this prediction, experimental findings in *D. simulans* crosses coupled with simulations show that *Wolbachia* can generate signals of intra-locus sexual conflict (Duffy *et al.,* 2019). This possibility is currently largely overlooked as a potentially common source generating sexual conflict in arthropods, but is likely to be of genuine importance seeing the prevalence of CI-inducing endosymbionts.

The uniparental inheritance of mitochondria, the powerhouse of cells, generates a conflict with the nuclear genome over sex determination and sex ratio, and also creates the opportunity for sexually antagonistic selection as mitochondria can increase maternal fitness but with a potential detrimental side-effect to males – often referred to as 'mothers curse' (Gemmell *et al.,* 2004; Havird *et al.,* 2019). This occurs because mtDNA cannot evolve for male function as their heritability in males is zero. For example, in dioecious plants there is evidence that mitochondria can induce cytoplasmic sterility and abort pollen production altogether, instead diverting these resources to enhance the female function which will favour mitochondrial transmission (e.g. Loussaert *et al.,* 2017). This generates selection on the nuclear genome to suppress the action of such selfish mitochondria and restore sex ratio to unity (Fujii *et al.,* 2011). Less overt is the situation where mitochondrial genes have a negative effect on male fitness that can include compromised sperm function and fertility without affecting female fitness (Patel *et al.,* 2016; Vaught & Dowling, 2018). Such reduced male reproductive fitness can persist, as low fertility genes are not removed by selection since they are inherited through females where they are never expressed. However, selfish mitochondria can also generate antagonistic selection by favouring the female function at a cost to male fitness. One such example is a mutation in the cytochrome B identified in *D. melanogaster* that increase female fitness whilst simultaneously decreasing male fertility (Camus *et al.,* 2018). It is therefore likely that selfish mitochondria also represent a ubiquitous source generating sexually antagonistic selection.

In summary, because of the asymmetrical inheritance of many SGEs, it is perhaps not surprising they often generate sex-specific fitness impacts. There is extensive evidence that maternally inherited cytoplasmic SGEs can generate sex-specific and sexually antagonistic selection. Future research will reveal the relative importance of endosymbionts such as *Wolbachia* and the mitochondria for generating sex-specific selection, but it is worth noting that the inheritance patterns will promote genetic hitchhiking between these two cytoplasmic agents eventually resulting in linkage. Similarly, the frequently reported nuclear-mitochondrial interactions affecting male fertility may be due to endosymbionts such as *Wolbachia, Spiroplasma* and *Cardinium*, rather than a linkage disequilibrium between certain maternal mitochondrial haplotypes and the nuclear genome. Hence, endosymbionts may have an overlooked role to play in generating the reported 'mitochondrial load' reducing male fertility reported in several insects. The origin of mitochondria stems from an ancient endosymbiosis, and hence share features with other endosymbionts, albeit subject to billion years of coevolution (Zachar *et al.,* 2018). It is therefore possible there are lessons to be learnt from studying coevolved associations of different ages to explore the importance of the interactions between nuclear and cytoplasmic genes for the pattern of sex-specific and sexually antagonistic effects and the potential for resolution of such SGE-generated sexual conflicts.

b) Sex-ratio distorters are sex-specific and can generate conflict

Most sex ratio distorters target males by killing sperm, males, or by feminization of genetic males, and inducing parthenogenesis and therefore by their very nature, generate strong sex-specific effects. There are examples of sex-ratio distorters that bias sex ratio towards males such as *psr* in *Nasonia* wasps that convert diploid eggs into haploid eggs resulting in male offspring. Nevertheless, despite being paternally inherited, this results in complete elimination of the sperm-derived hereditary material (Aldrich *et al.,* 2017). Paternal genome elimination (PGE) also occurs in mealybugs where males are diploid but only transmit the maternally inherited chromosomes with the paternal ones eliminated from their sperm (Normark, 2003). As a consequence, mothers in effect monopolise the parentage of sons at the cost of fathers' reproductive success generating a conflict between maternal and paternal genomes over gene transmission. PGE is a type of meiotic drive in which the entire maternal chromosomal complement drives, and hence we expect there to be strong selection for suppression of PGE to evolve as is the case in many other meiotic drive systems (Jaenike, 2001). Crosses between *Planococcus citri* and *P. ficus* mealybugs have the potential to uncover such an arms-race between maternal and paternal chromosomes. Recent experiments revealed that elimination of paternally derived chromosomes was not completely effective, implying scope for intragenomic conflict, but no evidence for an ongoing arms race was found (de la Filia *et al.,* 2019). As yet, it is not known if the incomplete PGE is associated with any fitness differences between male genotypes, but it would appear that there is almost complete maternal control over inheritance. Less extreme examples of sex ratio distorters exerting sex-specific selection are found in other taxa harbouring sperm and male killers, and feminizers.

Above, I have provided several examples of SGEs generating sexual selection and sexual conflict and also outlined why we might expect this to be the case, i.e. asymmetrical inheritance and the generation of sex-specific selection. There are several similarities between the conflict generated by segregation distorters such as meiotic drivers and sexually antagonistic alleles (SA, alleles with opposing fitness effects when expressed in males and females) that stem from the reproductive conflict between the two sexes (Trivers & Burt, 2006). A recent model has even shown that meiotic drive attracts SA alleles and can increase

485 the opportunity for polymorphism, and similarly that the opportunity for polymorphism at a
486 driving locus also increases when linked to a SA locus (Patten, 2014). The initial model was
487 developed for autosomal drive but the findings also holds true for X-linked drive: the driving
488 sex chromosome becomes enriched for sexually antagonistic effects that benefits the sex in
489 which the drive occurs (Rydzewski *et al.,* 2016). Both processes have the potential to
490 maintain genetic variation within populations, but to date there has been little empirical
491 exploration into the possibility that meiotic drive and sexually antagonistic selection
492 stemming from SA alleles can reinforce each other and contribute to genetic variation of
493 fitness related traits.
494
495 The frequency of drive alleles is predicted to increase when a drive allele is linked to a
496 sexually antagonistic polymorphism. In addition, drivers are predicted to accumulate SA
497 alleles and to favour reduced recombination, analogous to a sex-determining locus (Patten,
498 2014; Rydzewski *et al.,* 2016). Previous models have shown that sexual antagonism should in
499 itself favour reduced recombination (Rice, 1987) hence the combined impact of drive and
500 sexual antagonism should strengthen the speed of evolution of reduced recombination
501 (Patten, 2014; Rydzewski *et al.,* 2016). We therefore predict that there should commonly be
502 haplotypes with driving and sexually antagonistic effects that in theory should promote new
503 sex-determining alleles. This is especially true for meiotic drivers with strong sex-specific
504 fitness effects that may give rise to new sex determining alleles. It is known that sex
505 chromosomes are particularly vulnerable to the invasion of drivers (Jaenike, 2001), but
506 maybe drivers themselves have an unappreciated role to play in the origin of new sex
507 chromosomes (Kozielska *et al.,* 2010; Patten, 2014).
508
509 In summary, sex-linked meiotic drivers and sexual antagonism appear to be intrinsically
510 linked and their joint selective force may exert dramatic impact on sex chromosome
511 evolution and fuel sexual conflict. This is especially likely to be the case when involving X-
512 chromosome drivers (Rydzewski *et al.,* 2016). Drive is more likely to occur on the X
513 chromosome than on the autosome (Jaenike, 2001), and the X chromosome is predicted to
514 accumulate SA alleles (Rice, 1987). Hence, there is a predicted link between sexual
515 antagonism, meiotic drive and sex determination – any one of them will favour the other two
516 in a population (Patten, 2014).
517
518 *c) Other SGEs as sexually antagonistic alleles*
519 Segregation distorters are unequally exposed to selection in males and females, a trait they
520 have in common with SA alleles. While many SGEs such as segregation distorters act
521 through brute force via killing of males and sperm, or through feminization of genetic males
522 resulting in sex-bias, other SGEs are inherited equally through males and females such as
523 TEs and exert a more subtle sex-specific effect. It is worth remembering that the transmission
524 success of TEs is reliant on sex, as sexual reproduction and outcrossing provide TEs with a
525 means of spreading to all individuals in a population (Wright & Finnegan, 2001). This
526 prediction is supported by findings that in yeast asexual reproduction is shown to reduce the
527 load of TEs (Bast *et al.,* 2019). In mammals, it appears that oocytes are more resilient to TE
528 activity than the male germline, and it is suggested that this difference could be due to the
529 ongoing division of sperm cells, in contrast to oocytes, which undergo a long meiotic arrest.
530 Cell division is required for TE transposition, and many more cell divisions occur in the male
531 germline (Dechaud *et al.,* 2019). But there are also sex-differences in expression patterns of
532 TEs that affect reproductive fitness. For example, in *D. melanogaster* insecticide resistance is
533 due to the action of a TE element inserted into the promotor region of a P450 detoxification
534 gene (*Cyp6g1*) that result in upregulation and resistance (ffrench-Constant, 2013).

Interestingly there are large sex-differences in the expression pattern of the TE-generated insecticide resistance allele with females showing greater expression and greater resistance to insecticides compared to males (Schmidt *et al.,* 2010). Even without the TE insertion there appear to be sex differences in the expression pattern of *Cyp6g1* (Catalan *et al.,* 2012). Importantly, these sex-differences in expression are associated with sex-specific fitness differences depending of the genetic background. In most genetic backgrounds examined, resistant females enjoy a fecundity advantage compared to their susceptible counterparts implying no cost to resistance (McCart *et al.,* 2005; Rostant *et al.,* 2015; Hawkes *et al.,* 2016). In contrast, in males increased expression of *Cyp6g1* conferring resistance can be associated with large fitness costs in terms of reduced mating success and reproductive output (Smith *et al.,* 2011; Hawkes *et al.,* 2016; Rostant *et al.,* 2017). In other words, the resistance allele functions as a SA allele conferring high fitness females and low fitness males and this sex-difference in fitness is sufficient to maintain polymorphism at this locus (Rostant *et al.,* 2015). As yet it is not clear if the differential expression of *Cyp6g1* due to the TE activity between the sexes is an outcome to reduce the detrimental SA effects in males, or is an intrinsic effect of TE activity. But it is remarkable what large-scale impact upregulation of one gene has on the behaviour, morphology and fitness of *D. melanogaster* flies indicating substantial pleiotropic effects of this gene (Rostant *et al.,* 2017). Seeing that TEs are present in both bacteria and eukaryotes and can dramatically affect expression of individual genes and gene networks, often in a sex specific manner, it is highly likely there will be many more examples of TEs with sexually antagonistic effects to be discovered.

5. Summary and future prospects

The selfish nature of SGEs generates conflict with the rest of the genome that will select for suppression and silencing of selfishness. This is especially true for SGEs causing sex ratio distortion, that in turn can promote the evolution of new sex chromosomes. However, changes to sex determination, such as going from male heterogamety to female heterogamety or *vice versa* will alter the opportunity for selection. Heterogamety exposes recessive alleles to selection and therefore generates differential selection on sex-linked genes expressed in males and females (Rice, 1984). In principle, any SGE that is already present on a sex chromosome (or on a former autosome now involved in sex determination) will experience a shift in the strength of sex-specific selection. And as mentioned, segregation distorters such as sex-linked meiotic drivers are themselves magnets for SA alleles and hence are expected to accumulate on the driving sex chromosome (Rydzewski *et al.,* 2016). Many SGEs associated with sex ratio bias may therefore have dramatically different fitness effects when expressed in males or females following a shift in sex determination, depending on the population sex ratio and the degree of sex bias. For example, a genome that has experienced extensive periods of feminizing selection (e.g. by feminizing, male killing, or parthenogenesis-inducing bacteria) may have accumulated female-benefit alleles that lower male fitness when expressed in "rescued" males after the evolution of suppressors of sex-ratio distortion. We may predict that over time the cost of expressing such newly exposed SA alleles in the "rescued" sex should be ameliorated (Bonduriansky & Chenoweth, 2009). The resurgence of SA alleles may therefore be more prominent in populations experiencing a recent spread of a segregation-distorting suppressor allele or a shift in sex determination. In general, the rapid turn-over of sex chromosomes generated by sex ratio distorters will alter the exposure of sex-linked SA alleles to selection and contribute to sexual conflict. Seeing that sex chromosomes are magnets for SGEs and SA alleles, and in turn SGEs promote sex

chromosome turnover, there is a direct link between the recurrent intragenomic conflict caused by SGEs and the resurgence and exposure of SA alleles on sex chromosomes.

SGEs may also represent an overlooked source generating balancing selection. Theory shows that because of the predicted tight linkage that is expected to accumulate between segregation distorters and SA alleles, they will contribute to increased polymorphism at driving and SA loci and thus maintain overall genetic variation (Patten, 2014). However, also non-driving SGEs have the potential to maintain genetic variation in sexually selected traits by generating strong opposing selection. For example, feminizing endosymbionts have the potential to expose male genomes to extensive feminizing selection that could compromise trait expression when males eventually escape feminization through naturally occurring curing events. As yet there is no definitive verification of this suggestion although preliminary findings indicate that male ultra-violet wing colouration – a sexually selected trait in male *Eurema hecabe* butterflies - is eroded when exposed to feminizing selection caused by a maternally-inherited female-biasing agent (Wedell & Kemp, *unpubl.*). Future work will reveal to what extent this reduction in male trait value is directly due to feminizing selection imposed by the endosymbiont, and therefore raises the possibility it may balance the increased trait value favoured by female choice (Kemp, 2008).

In this review I have outlined several ways in which SGEs can directly shape sexual selection and sexual conflict by promoting sex chromosome evolution (e.g. sex-ratio distorters), affecting gene expression of sex-linked genes with SA effects (e.g. TEs), generating strong sex-specific selection (e.g. maternally transmitted endosymbionts and mitochondria) and acting as a magnet for SA alleles (e.g. segregation distorters). It is likely that there are many more undetected cases of SGEs with the potential to generate sexual selection and sexual conflict, but that have largely gone undetected (Lindholm *et al.,* 2016). Genetic conflict that involves antagonistic coevolution of SGEs and suppressors are often only uncovered in interpopulation crosses. Seeing the prevalence of SGEs in nature, this source of sexual conflict is likely to be greatly overlooked.

Acknowledgments
I thank Professor Nigel Bennett and the Editorial Board for the honour and opportunity to write this review. I also thank Professor David Hosken for his encouragement and sharing his insights, and Professors Hosken and Pizzari and three anonymous referees for the very helpful comments on the MS.

References

Albertson, R., Tan, V., Leads, R.R. *et al.* (2013). Mapping *Wolbachia* distributions in the adult *Drosophila* brain. *Cell Microbiol*. **15,** 1527–1544.

Ahola, V., Lehtonen, R., Somervuo, P., Salmela, L., Koskinen, P., Rastas, P., Välimäki, N., Paulin, L., Kvist, J., Wahlberg, N., Tanskanen, J., Hornett, E.A., Fergusen, L.C., Luo, S., Cao, Z., de Jong, M.A., Duploy, A., Smolander, O-P., Vogel, H., McCoy, R.C., Qian, K., Chong, W.S., Zhang, Q., Ahmad, F., Haukka, J.K., Joshi, A., Salojärvi, J., Wheat, C.W., Grosse-Wilde, E., Hughes, D., Katainen, R., Pitkänen, E., Ylinen, J., Waterhouse, R.M., Turunen, M., Vähärautio, A., Ojanen, S.P., Schulman, A.H., Taipale, M., Lawson, D., Ukkonen, E., Mäkinen, V., Goldsmith, M.R., Holm, L., Auvinen, P., Frilander, M.J. & Hanski, I. (2014). The Glanville fritillary genome retains an ancient karyotype and reveals selective chromosomal fusions in Lepidoptera. *Nature Comm.* **5,** 4737.

Aldrich, J.C., Leibholz, A., Cheema, M.S., Ausio, J. & Ferree, P.M. (2017). A 'selfish' B chromosome induces genome elimination by disrupting the histone code in the jewel wasp *Nasonia vitripennis*. *Sci. Rep.* **13**, 42551. doi: 10.1038/srep42551.

Angelard, C., Montchamp-Moreau, C. & Joly, D. (2008). Female driven mechanisms, ejaculate size and quality contribute to the lower fertility of *sex-ratio* distorter males in *Drosophila simulans*. *BMC Evol. Biol.* **8,** 326. doi: 10.1186/1471-2148-8-326.

Arburthnott, D., Levin, T.C., & Promislow, D.E. (2016). The impacts of *Wolbachia a*nd the microbiome on mate choice in *Drosophila melanogaster*. *J. Evol. Biol*. **29,** 461–468.

Bast, J., Jaron, K.S., Schiseil, D., Roze, D. & Schwander, T. (2019). Asexual reproduction reduces transposable element load in experimental yeast populations. *eLife* **8,** e48548. doi: 10.7554/eLife.48548.

Beeman, R., Friesen, K. & Denell, R. (1992). Maternal-effect selfish genes in flour beetles. *Science* **256,** 89–92.

Bell, A., Brunt, J., Crost, E. *et al.* (2019). Elucidation of a sialic acid metabolism pathway in mucus-foraging *Ruminococcus gnavus* unravels mechanisms of bacterial adaptation to the gut. *Nature Microbiol.* **4,** 2393–2404.

Beukeboom, L.W. & Perrin, N. (2014). *The Evolution of Sex Determination*. Oxford University Press.

Bird, A. (2020). The selfishness of law-abiding genes. *Trends Genet.* **36,** 1 doi.org/10.1016/ j.tig.2019.10.002

Burt, A. & Trivers, R. (2006). *Genes in Conflict*. Belknap Press of Harvard University Press, Cambridge, MA.

Bonduriansky, R. & Chenoweth, S.F. (2009). Intralocus sexual conflict. *Trends Ecol. Evol.* **24,** 280–288.

671 Camus, M.F. & Dowling, D.K. (2018). Mitochondrial genetic effects on reproductive
672 success: signatures of positive intrasexual, but negative intersexual pleiotropy. *Proc. R. Soc.*
673 *Lond. B* **285,** 20180187.
674
675 Chafee, M.E. (2011). Decoupling of host–phage coadaptations following transfer between
676 insect species. *Genetics* **187,** 203–215.
677
678 Champion de Crespigny, F.E. & Wedell, N. (2006). *Wolbachia* infection reduces sperm
679 competitive ability in an insect. *Proc. R. Soc. Lond. B* **273,** 1455-1458.
680
681 Champion de Crespigny, F.E. & Wedell, N. (2007). Mate preferences in *Wolbachia* infected
682 *Drosophila*. *Behav. Ecol. Sociobiol.* **61,** 1229-1235.
683
684 Carabel Paladio, L.Z., Provaznikova, I., Befrger, M., Bass, C., Aratchige, N.S., Lopez, S.N.,
685 Marec, F. & Nguyen, P. (2019). Sex chromosome turnover in moths of the diverse
686 superfamily *Gelechioidea*. *Genome Biol. Evol.* **11,** 1307-1319.
687
688 Catalan, A., Hutter, S. & Parch, J. (2012). Population and sex differences in *Drosophila*
689 *melanogaster* brain gene expression. *BMC Genomics* **13,** 654.
690
691 Chmatal, L., Gabriel, S.I., Mitsainas, G.P., Martinez-Vargas, J., Ventura, J., Searle, J.B.,
692 Schultz, R.M., & Lampson, M.A. (2014). Centromere strength provides the cell biological
693 basis for meiotic drive and karyotype evolution in mice. *Curr. Biol.* **24,** 2295–2300.
694
695 Cotton, A.J., Foldvari, M., Cotton, S. & Pomiankowski, A. (2014). Male eye span size is
696 associated with meiotic drive in wild stalk-eyed flies (*Teleopsis dalmanni*). *Heredity* **112,**
697 363-369.
698
699 Courret, C., Chang, C.-H., Wei, K.H.-C., Montchamp-Moreau, C. & Larracuente, A.M.
700 (2019). Meiotic drive mechanisms: lessons from *Drosophila*. *Proc. R. Soc. Lond. B* **286**,
701 20191430.
702
703 Dechaud, C., Volff, J.-N., Schartl, M. & Naville, M. (2019). Sex and the TEs: transposable
704 elements in sexual development and function in animals. *Mobile DNA* **10,** 42
705 doi.org/10.1186/s13100-019-0185-0.
706
707 Dedeine, F., Vavre, F., Fleury, F., Loppin, B., Hochberg, M.E. & Boulétreau, M. (2001).
708 Removing symbiotic *Wolbachia* bacteria specifically inhibits oogenesis in a parasitic wasp.
709 *Proc. Natl. Acad. Sci.* **98,** 6247–6252.
710
711 De la Filia, A.G., Fenn-Moltu, G. & Ross, L. (2019). No evidence for an intragenomic arms
712 race under paternal genome elimination in *Planococcus* mealybugs. *J. Evol. Biol*. **32,** 491-
713 504.
714
715 Duffy, E., Archer, C.R., Sharma, M.D., Prus, M., Joag, R., Radwan, J., Wedell, N. & Hosken,
716 D. 2019. *Wolbachia* infection can bias estimates of intralocus sexual conflict. *Ecol. Evol.* **9,**
717 328-338.
718
719 Dunn, A.M., Terry, R.S. & Smith, J.E. (2001). Transovarial transmission in the
720 *Microsporidia*. *Adv. Parasitol.* **48,** 57-100.

Eberhard, W.G. (1996). *Female Control: Sexual Selection by Cryptic Female Choice*. Princeton University Press.

Engels, W.R. (1997). Invasions of P elements. *Genetics* **145,** 11–5.

Engl, T. & Kaltenpoth, M. (2018). Influence of microbial symbionts on insect pheromones. *Nat. Prod. Rep.* **35,** 386–397

ffrench-Constant, R.H. (2013). The molecular genetics of insecticide resistance. *Genetics* **194**, 807–815.

Fujii, S., Bond, C.S., & Small, I.D. (2011). Selection patterns on restorer-like genes reveal a conflict between nuclear and mitochondrial genomes throughout angiosperm evolution. *Proc. Natl. Acad. Sci.* **108,** 1723–1728.

Gemmell, N.J., Metcalf, V.J., & Allendorf, F.W. (2004). Mother's curse: the effect of mtDNA on individual fitness and population viability. *Trends Ecol. Evol.* **19,** 238–244.

Hall, D.W. (2004). Meiotic drive and sex chromosome cycling. *Evolution* **58,** 925–931.

Hamilton, W.D. (1967). Extraordinary sex ratios. *Science* **156,** 477–488.

Hammerberg, C. & Klein, J.A.N. (1975). Evidence for postmeiotic effect of *t* factors causing segregation distortion in mouse. *Nature* **253,** 137–138.

Havecker, E.R., Gao, X. & Voytas, D.F. (2004). The diversity of LTR retrotransposons. *Genome Biol.* **5,** 225.

Havird, J. C., Forsythe, E. S., Williams, A. M., Werren, J. H., Dowling, D. K. & Sloan, D. B. (2019). Selfish mitonuclear conflict. *Curr. Biol.* **29,** R496-R511.

Hawkes, M.F., Gamble, C.E., Turner, E.C.R., Carey, M.R., Wedell, N. & Hosken, D.J. (2016). Intralocus sexual conflict and insecticide resistance. *Proc R Soc Lond B* **283,** 20161429

Jaenike, J. (2001). Sex chromosome meiotic drive. *Annu. Rev. Ecol. Syst.* **32,** 25–49.

Johns, P.M., Wolfenbarger, L.L. & Wilkinson, G.S. (2005). Genetic linkage between a sexually selected trait and X chromosome meiotic drive. *Proc. R. Soc. Lond. B* **272,** 2097–2103.

Jurica, M.S. & Stoddard, B.L. (1999). Homing endonucleases: structure, function and evolution. *Cell. Mol. Life Sci.* **55,** 1304–1326.

Kageyama, D., Narita, S. & Watanabe, M. (2012). Insect sex determination manipulated by their endosymbionts: incidences, mechanisms and implications. *Insects* **3,** 161-199.

Keller, L. & Ross, K.G. (1998). Selfish genes: a green beard in the red fire ant. *Nature* **394,** 573-575.

Kemp, D.J. (2008). Female mating biased for bright ultraviolet iridescence in the butterfly *Eurema hecabe* (Pieridae). *Behav. Ecol.* **19,** 1-8.

Kitano, J. & Peichel, C.L. (2012). Turnover of sex chromosomes and speciation in fishes. *Env. Biol. Fishes* **94,** 549-558.

Koonin, E.V. & Dolja, V.V. (2014). Virus world as an evolutionary network of viruses and capsidless selfish elements. *Microbiol. Mol. Biol. Rev.* **78,** 278-303.

Kozielska, M., Weissing, F.J., Beukeboom, L.W. & Pen, I. (2010). Segregation distortion and the evolution of sex-determining mechanisms. *Heredity* **104,** 100–112.

Lande, R. & Wilkinson, G. S. (1999). Models of sex-ratio meiotic drive and sexual selection in stalk-eyed flies. *Genet. Res.* **74,** 245–253.

Lander, E.S., Linton, L.M., Birren, B., Nusbaum, C., Zody, M.C., Baldwin, J., Devon, K., Dewar, K., Doyle, M., FitzHugh, W., Funke, R., Gage, D., Harris, K., Heaford, A., Howland, J., Kann, L., Lehoczky, J., LeVine, R., McEwan, P., McKernan, K., Meldrim, J., Mesirov, J.P., Miranda, C., Morris, W., Naylor, J., Raymond, C., Rosetti, M., Santos, R., Sheridan, A., Sougnez, C., Stange-Thomann, Y., Stojanovic, N., Subramanian, A., Wyman, D., Rogers, J., Sulston, J., Ainscough, R., Beck, S., Bentley, D., Burton, J., Clee, C., Carter, N., Coulson, A., Deadman, R., Deloukas, P., Dunham, A., Dunham, I., Durbin, R., French, L., Grafham, D., Gregory, S., Hubbard, T., Humphray, S., Hunt, A., Jones, M., Lloyd, C., McMurray, A., Matthews, L., Mercer, S., Milne, S., Mullikin, J.C., Mungall, A., Plumb, R., Ross, M., Shownkeen, R., Sims, S., Waterston, R.H., Wilson, R.K., Hillier, L.W., McPherson, J.D., Marra, M.A., Mardis, E.R., Fulton, L.A., Chinwalla, A.T., Pepin, K.H., Gish, W.R., Chissoe, S.L., Wendl, M.C., Delehaunty, K.D., Miner, T.L, Delehaunty, A., Kramer, J.B., Cook, L.L., Fulton, R.S., Johnson, D.L., Minx, P.J., Clifton, S.W., Hawkins, T., Branscomb, E., Predki, P., Richardson, P., Wenning, S., Slezak, T., Doggett, N., Cheng, J.F., Olsen, A., Lucas, S., Elkin, C., Uberbacher, E., Frazier, M., Gibbs, R.A., Muzny, D.M., Scherer, S.E., Bouck, J.B., Sodergren, E.J., Worley, K.C., Rives, C.M., Gorrell, J.H., Metzker, M.L., Naylor, S.L., Kucherlapati, R.S., Nelson, D.L., Weinstock, G.M., Sakaki, Y., Fujiyama, A., Hattori, M., Yada, T., Toyoda, A., Itoh, T., Kawagoe, C., Watanabe, H., Totoki, Y., Taylor, T., Weissenbach, J., Heilig, R., Saurin, W., Artiguenave, F., Brottier, P., Bruls, T., Pelletier, E., Robert, C., Wincker, P., Smith, D.R., Doucette-Stamm, L., Rubenfield, M., Weinstock, K., Lee, H.M., Dubois, J., Rosenthal, A., Platzer, M., Nyakatura, G., Taudien, S., Rump, A., Yang, H., Yu, J., Wang, J., Huang, G., Gu, J., Hood, L., Rowen, L., Madan, A., Qin, S., Davis, R.W., Federspiel, N.A., Abola, A.P., Proctor, M.J., Myers, R.M., Schmutz, J., Dickson, M., Grimwood, J., Cox, D.R., Olson, M.V., Kaul, R., Raymond, C., Shimizu, N., Kawasaki, K., Minoshima, S., Evans, G.A., Athanasiou, M., Schultz, R., Roe, B.A., Chen, F., Pan, H., Ramser, J., Lehrach, H., Reinhardt, R., McCombie, W.R., de la Bastide, M., Dedhia, N., Blöcker, H., Hornischer, K., Nordsiek, G., Agarwala, R., Aravind, L., Bailey, J.A., Bateman, A., Batzoglou, S., Birney, E., Bork, P., Brown, D.G., Burge, C.B., Cerutti, L., Chen, H.C., Church, D., Clamp, M., Copley, R.R., Doerks, T., Eddy, S.R., Eichler, E.E., Furey, T.S., Galagan, J., Gilbert, J.G., Harmon, C., Hayashizaki, Y., Haussler, D., Hermjakob, H., Hokamp, K., Jang, W., Johnson, L.S., Jones, T.A., Kasif, S., Kaspryzk, A., Kennedy, S., Kent, W.J., Kitts, P., Koonin, E.V., Korf, I., Kulp, D., Lancet, D., Lowe, T.M., McLysaght, A., Mikkelsen, T., Moran, J.V., Mulder, N., Pollara, V.J., Ponting, C.P., Schuler, G., Schultz, J., Slater, G., Smit, A.F., Stupka, E., Szustakowki, J., Thierry-Mieg, D., Thierry-

Mieg, J., Wagner, L., Wallis, J., Wheeler, R., Williams, A., Wolf, Y.I., Wolfe, K.H., Yang, S.P., Yeh, R.F., Collins, F., Guyer, M.S., Peterson, J., Felsenfeld, A., Wetterstrand, K.A., Patrinos, A., Morgan, M.J., de Jong, P., Catanese, J.J., Osoegawa, K., Shizuya, H., Choi, S., Chen, Y.J., Szustakowki, J. & International Human Genome Sequencing Consortium. (2001). Initial sequencing and analysis of the human genome. *Nature* **409,** 860-921.

Leclerqc, S., Thézé, J., Chebbi, M.A., Giraud, I., Moumen, B., Ernenwein, L., Grève, P., Gilbert, C. & Cordaux, R. (2016). Birth of a W sex chromosome by horizontal transfer of *Wolbachia* bacterial symbiont genome. *Proc. Natl. Acad. Sci.* **113,** 15036-15041.

Lenington, S. (1991). The *t*-complex: a story of genes, behavior, and populations. *Adv. Study Behav.* **20,** 51–86.

Lima, T.G. (2014). Higher level of sex chromosome heteromorphism are associated with markedly stronger reproductive isolation. *Nature Comm.* **5,** 4743.

Lindholm, A.K., Musolf, K., Weidt, A. & Konig, B. (2013). Mate choice for genetic compatibility in the house mouse. *Ecol. Evol.* **3,** 1231–1247.

Lindholm A.K. Dyer K.A., Firman R.C., Fishman L., Forstmeier W., Holman L., Johannesson H., Knief U., Kokko H., Larracuente A.M., Manser A., Montchamp-Moreau C., PetrosyanV.G., Pomiankowski A., Presgraves D.C., Safronova L.D., Sutter A., Unckless R.L., Verspoor R.L., Wedell N., Wilkinson G.S., and Price T.A.R. (2016). The ecology and evolutionary dynamics of meiotic drive. *Trends Ecol. Evol.* **31,** 315-326.

Loussaert, D., DeBruin, J., San Martin, J.P., Schussler, J., Pape, R., Clapp, J., Mongar, N., Fox, T., Albertsen, M., Trimnell, M., Collinson, S & Shen, B. (2017). Genetic male sterility (Ms44) Increases maize grain yield. *Crop. Sci*. **57,** 2718–2728.

Lyttle, T.W. (1981). Experimental population genetics of meiotic drive systems III. Neutralization of sex ratio distortion in *Drosophila* through sex chromosome aneuploidy. *Genetics* **98,** 317-334.

Ma, W.-J., Vavre, F. & Beukeboom, L.W. (2014). Endosymbiotic manipulation of arthropod sex determination: diversity and molecular mechanisms. *Sex. Dev.* **8,** 59–73.

Mank, J., Hosken, D.J. & Wedell, N. (2014). Conflict on the sex chromosomes: cause, effect, and complexity. In: *Sexual Conflict*. 341-354. Rice, W.R. & Gavrilets, S. (Eds.) Cold Spring Harbor Press.

Manser, A., Lindholm, A.K. & Weissing, F.J. (2017). The evolution of costly mate choice against segregation distorters. *Evolution* **71,** 2817-2828.

Martin, S.M., Singh, K.S., Gordon, I.J., Omufwoko, K.S., Collins, S., Warren, I.A., Munby, H., Brattstrom, O., Traut, W., Martins, D.J., Smith, D.A.S., Jiggins, C.D., Bass, C. & ffrench-Constant, R.H. (2020). Whole-chromosome hitchhiking driven by a male-killing endosymbiont. *PLos Biol.* **18**, e3000610.

McCart, C., Buckling, A. & ffrench-Constant, R.H. (2005). DDT resistance in flies carries no cost. *Curr. Biol.* **15,** R587-589.

Meade, L.C., Dinneen, D., Kad, R., Lynch, D.M., Fowler, K. & Pomiankowski. A. (2019). Ejaculate sperm number compensation in stalked-eyed flies carrying a selfish meiotic drive element. *Heredity* **122,** 916–926.

Meade, L.C., Finnegan, S.R., D.M., Kad, R., Fowler, K. & Pomiankowski. A. 2020. Maintenance of fertility in the face of meiotic drive. Am. Nat. doi.org/10.1086/707372.

Meiklejohn, C.D. & Tao, Y. (2009). Genetic conflict and sex chromosome evolution. *Trends Ecol. Evol.* **25,** 215–223.

Miller, W.J., Ehrman, L. & Schneider, D. 2010. Infectious speciation revisited: impact of symbiont-depletion on female fitness and mating behavior of *Drosophila paulistorum*. *PLoS Path*. **6,** e1001214.

Miyata, M., Konagaya, T., Yukuhiro, K., Nomura, M. & Kageyama, D. (2017). *Wolbachia*-induced meiotic drive and feminization is associated with an independent occurrence of selective mitochondrial sweep in a butterfly. *Biol. Lett.* **13,** 20170153.

Nichols, R.A. & Butlin, R.K. (1998). Does runaway sexual selection work in finite populations. *J. Evol. Biol.* **2,** 299–313.

Nolte, V., Pandey, R.M., Kofler, R. & Schlotterer, C. (2013). Genome-wide patterns of natural variation reveal strong selective sweeps and ongoing genomic conflict in *Drosophila mauritiana*. *Genome Res.* **23,** 99–110.

Normark, B. B. (2003). The evolution of alternative genetic systems in insects. *Ann. Rev. Entomol.* **48,** 397–423.

Patel, M.R., Miriyala, G.K., Littleton, A.J., Yang, H.K., Trinh, K., Young, J.M., Kennedy, S.R., Yamashita, Y.M., Pallanck, L.J., & Malik, H.S. (2016). A mitochondrial DNA hypomorph of cytochrome oxidase specifically impairs male fertility in *Drosophila melanogaster*. *eLife* **5,** e16923.

Parker, G.A. (1970). Sperm competition and its evolutionary consequences in insects. *Biol. Rev.* **45,** 525-567.

Patten, M.M. (2014). Meiotic drive influences the outcome of sexually antagonistic selection at a linked locus. *J. Evol. Biol.* **27,** 2360–2370.

Pizzari, T. & Birkhead, T.R. (2000). Female fowl eject sperm of subdominant males. *Nature* **405,** 787-789.

Price, T.A.R. & Wedell, N. (2008). Selfish genetic elements and sexual selection: their impact on male fertility. *Genetica* **132,** 295–307.

Price, T.A.R., Bretman, A.J., Avent, T., Snook, R.R., Hurst, G.D.D. & Wedell, N. (2008a). Sex ratio distorter reduces sperm competitive ability in an insect. *Evolution* **62,** 1644-1652.

916 Price, T.A.R., Hodgson, D.J., Lewis, Z., Hurst, G.D.D. & Wedell, N. (2008b). Selfish genetic
917 elements promote polyandry in a fly. *Science* **322,** 1241-1243.
918
919 Price, T.A.R., Lewis, Z. & Wedell, N. (2009). Sperm dumping as a defense against meiotic
920 drive. *J. Biol.* **8**, 6 doi:10.1186/jbiol109.
921
922 Price, T.A.R., Hurst, G.D.D. & Wedell, N. (2010). Polyandry prevents extinction. *Curr. Biol.*
923 **20,** 471–475.
924
925 Price, T.A.R., Lewis, Z., Smith, D.T., Hurst, G.D.D. & Wedell, N. (2012). No evidence of
926 mate discrimination against males carrying a sex ratio distorter in *Drosophila pseudoobscura.*
927 *Behav. Ecol. Sociobiol.* **66,** 561-568.
928
929 Randerson, J.P. & Hurst, L.D. (1999). Small sperm, uniparental inheritance and selfish
930 cytoplasmic elements: a comparison of two models. *J. Evol. Biol.* **12,** 1110-1124.
931
932 Rice, W.R. (1984). Sex chromosomes and the evolution of sexual dimorphism. *Evolution* **38,**
933 735–742.
934
935 Rice, W.R. (1987). The accumulation of sexually antagonistic genes as a selective agent
936 promoting the evolution of reduced recombination between primitive sex chromosomes.
937 *Evolution* **41,** 911–914.
938
939 Richard, F.-J. (2017). Symbiotic bacteria influence the odor and mating preference of their
940 host. *Front. Ecol. Evol.* **5,** 143.
941
942 Rigaud, T. (1997) Inherited microorganisms and sex determination of arthropod hosts. In:
943 *Influential Passengers: Inherited Microorganisms and Arthropod Reproduction:* 81-101.
944 O'Neill, S.L., Hoffmann, A.A. & Werren, J.H. (Eds). New York: Oxford Univ. Press
945
946 Rostant, W.G., Kay, C., Wedell, N. & Hosken, D.J. (2015). Sexual conflict maintains
947 variation at an insecticide resistance locus. *BMC Biol*. **13,** 34.
948
949 Rostant, W.G., Bowyer, J., Coupland, J., Facey, J., Hosken, D.J. & Wedell, N. (2017).
950 Pleiotropic fitness effects of DDT resistance of male size and behavior. *Behav. Genet.* **47**,
951 449-458.
952
953 Rydzewski, E.T., Carioscia, S.A., Lievano, G., Lynch, V.D. & Patten, M.M. (2016). Sexual
954 antagonism and meiotic drive cause stable linkage disequilibrium and favour reduced
955 recombination on the X chromosome. *J. Evol. Biol*. **29,** 1247–1256.
956
957 Schmidt, J.M., Good, R.T., Appleton, B., Sherrard, J., Raymant, G.C., Bogwitz, M.R.,
958 Martin, J., Daborn, P.J., Goddard, M.E., Batterham, P., & Robin, C. (2010). Copy number
959 variation and transposable elements feature in recent, ongoing adaptation at the *Cyp6g1*
960 locus. *PLoS Genet*. **6**, e1000998.

961 Smillie, C., Garcillán-Barcia, M.P., Francia, M.V., Rocha, E.P.C. & de la Cruz, F. (2010).
962 Mobility of plasmids. *Microbiol. Mol. Biol. Rev.* **74,** 434–452.

963 Smith, D.T., Hosken, D.J., Rostant, W.G., Yeo, M., Griffin, R.M., Bretman, A., Price,
964 T.A.R., ffrench-Constant, R.H. & Wedell, N. (2011). DDT resistance, epistasis and male
965 fitness in flies. *J. Evol. Biol.* **24,** 1351-1362.

966 Snook, R.R. & Hosken, D.J. (2004). Sperm death and dumping in *Drosophila*. *Nature* **428,**
967 939-941.

968 Snook, R.R., Cleland, S.Y., Wolfner, M.F. & Karr, T.L. (2000). Offsetting effects of
969 Wolbachia infection and heat shock on sperm production in *Drosophila simulans*: analyses of
970 fecundity, fertility and accessory gland proteins. *Genetics* **155,** 167-178.
971
972 Strunov, A., Schneider, D.I., Albertson, R., and Miller,WJ. (2017). Restricted distribution
973 and lateralization of mutualistic *Wolbachia* in the *Drosophila* brain. *Cell. Microbiol.* **19**,
974 e12639.
975
976 Sutter, A. & Lindholm, A.K. (2016). No evidence for female discrimination against male
977 house mice carrying a selfish genetic element. *Curr. Zool.* **62,** 675–685.
978
979 Tomoatsu, I., Broughton, S., Nazif, Al., Grandison, R. & Partridge, L. (2009). The
980 endosymbiont *Wolbachia* increases insulin/IGF-like signalling in *Drosophila. Proc. R. Soc.*
981 *Lond. B.* **276,** http://doi.org/10.1098/rspb.2009.0778
982
983 Turelli, M. & Begun, D.J. (1997). Haldanes' rule and X-chromosome size in *Drosophila*.
984 *Genetics* **147,** 1799-1815.
985
986 Úbeda, F., Patten, M.M. & Wild. G. (2015). On the origin of sex chromosomes from meiotic
987 drive. *Proc. R. Soc. Lond. B* **282,** 20141932.
988
989 Vaught, R.C., & Dowling, D.K. (2018). Maternal inheritance of mitochondria: Implications
990 for male fertility? *Reproduction* **155,** R159-R168.

991 Vogan, A.A., Ament-Velásquez, S.L., Granger-Farbos, A., Svedberg, J., Bastiaans, E.,
992 Debets, A.J.M., Coustou, V., Yvanne, H., Clavé, C., Saupe, S.J. & Johannesson, H. (2019).
993 Combinations of *Spok* genes create multiple meiotic drivers in *Podospora. eLife* **8**, e46454.

994 Vogel, E., Santos, D., Mingels, L., Verdonckt, T.-W. & Broeck, J.V. (2019). RNA
995 interference in insects: protecting beneficials and controlling pests. *Front. Physiol.* **9,** 1912.
996 doi: 10.3389/fphys.2018.01912.
997
998 Wedell, N. (2013). The dynamic relationship between polyandry and selfish genetic
999 elements. *Phil. Trans. R. Soc. B* **368,** 20120049.
1000
1001 Wedell, N. (2019). The effect of non-self genes on the behaviour of hosts. In *Genes and*
1002 *Behaviour: Beyond Nature-Nurture*: 157-180. Hosken, D.J., Hunt, J. & Wedell, N. (Eds.)
1003 John Wiley & Sons.
1004
1005 Weeks, A.R., Turelli, M., Harcombe, W.R., Reynolds, K.T. & Hoffmann, A.A. (2007). From
1006 parasite to mutualist: rapid evolution of *Wolbachia* in natural populations of *Drosophila*.
1007 *PLoS Biol.* **5,** e177.
1008

Werren, J.H. (1991). The paternal sex-ratio chromosome of *Nasonia*. *Am. Nat.* **137,** 392-402.

Werren, J.H. (1997). The biology of *Wolbachia*. *Ann. Rev. Entomol.* **42,** 587–609.

Werren, J.H. (2011). Selfish genetic elements, genetic conflict, and evolutionary innovation. *Proc. Natl. Acad. Sci.* **108,** 10863–10870.

Wright, S, & Finnegan, D. (2001). Genome evolution: sex and the transposable element. *Curr. Biol.* **11,** R296-299.

Zachar, I., Szilagyi, A., Szamado, S. & Szathmary, E. (2018). Farming the mitochondrial ancestor as a model of endosymbiotic establishment by natural selection. *Proc. Natl. Acad. Sci.* **115,** E1504-E1510.

Zanders, S.E. & Unckless, R.L. (2019). Fertility costs of meiotic drivers. *Curr. Biol.* **29,** R512–R520.

Zeh, J.A. & Zeh, D.W. (1996). The evolution of polyandry I: intragenomic conflict and genetic incompatibility. *Proc. R. Soc. Lond. B* **263,** 1711-1717.

Zhou, Q. & Bachtrog, D. (2012). Chromosome-wide gene silencing initiate Y-degeneration in *Drosophila*. *Curr. Biol.* **22,** 522–525.