Cold Spring Harbor Perspectives in Biology
www.cshperspectives.org

Sexually Antagonistic Zygotic Drive: A New Form of Genetic Conflict between the Sex Chromosomes

Urban Friberg[1,2] and William R. Rice[3]

[1]Department of Evolutionary Biology, Uppsala University, 752 36 Uppsala, Sweden

[2]IFM Biology, Linköping University, 581 83 Linköping, Sweden

[3]Department of Ecology, Evolution and Marine Biology, University of California, Santa Barbara, California 93111

Correspondence: urban.friberg@liu.se

Sisters and brothers are completely unrelated with respect to the sex chromosomes they inherit from their heterogametic parent. This has the potential to result in a previously unappreciated form of genetic conflict between the sex chromosomes, called sexually antagonistic zygotic drive (SA-ZD). SA-ZD can arise whenever brothers and sisters compete over limited resources or there is brother–sister mating coupled with inbreeding depression. Although theory predicts that SA-ZD should be common and influence important evolutionary processes, there is little empirical evidence for its existence. Here we discuss the current understanding of SA-ZD, why it would be expected to elude empirical detection when present, and how it relates to other forms of genetic conflict.

When a diploid individual reproduces sexually, the two alleles at heterozygous loci are necessarily in competition because reproduction by one allele must be at the expense of the other. Such competition is an inescapable component of the organismal level of evolution that was originally advanced by Darwin and later integrated with the field of genetics during the modern synthesis of the early 20th century (Huxley 1942). If the competition is mediated by Mendelian segregation followed by (1) differences in the Darwinian fitness (i.e., survival and fecundity) that each allele produces in offspring, (2) random sampling (genetic drift), and/or (3) differences in the alleles' mutation or migration rates, then no genetic conflict exists and only canonical evolution at the organismal level occurs. But alleles can also compete outside the context of organismal evolution via diverse mechanisms of selection at the level of the gene that are collectively called genomic conflict (or selfish, ultraselfish, and parasitic DNA). These mechanisms can be divided into three general classes (Burt and Trivers 2006): (1) gonotaxis (in which the selfish elements bias Mendelian segregation by moving away from dead-end polar bodies and into the functional egg during oogenesis, i.e., meiotic or centromeric drive), (2) interference (in which the selfish element kills or debilitates noncarrier gam-

Editors: William R. Rice and Sergey Gavrilets
Additional Perspectives on The Genetics and Biology of Sexual Conflict available at www.cshperspectives.org

 doi: 101101/cshperspect.a017608
Cite this article as *Cold Spring Harb Perspect Biol* 2015;7:a017608

etes or offspring, i.e., segregation distortion and zygotic drive), and (3) overreplication (in which the selfish element increases its copy number in the genome, e.g., biased gene conversion, transposable elements, and homing endonucleases). De novo mutations can also gain a transmission advantage by increasing the rate of stem cell division in the germ line (germline drive) (e.g., Yoon et al. 2013). All of these genomic conflict mechanisms have been described in detail in Burt and Trivers (2006).

Genomic conflict frequently leads to reduced fitness at the organismal level. Meiotic drive can harm the organism as a whole because the attributes that provide a segregation advantage in oogenesis (e.g., the structure of the centromere and neighboring heterochromatin) can be maladaptive during spermatogenesis and contribute to male sterility (see, for review, Elde et al. 2011). Segregation distorters and zygotic drivers can substantially reduce a carrier male's fitness because they kill up to half of his sperm (leading to reduced fertility) and offspring, respectively. Sex-linked, meiotic drivers in WZ females (like birds) and segregation distorters and zygotic drivers in XY males (like insects and mammals) cause biased sex ratios that reduce fitness with respect to Fisherian sex ratio selection and can also reduce population growth and potentially drive species to extinction. Biased gene conversion and germline drive (Yoon et al. 2013) reduce organismal fitness when harmful mutations accumulate to elevated levels (i.e., beyond the conventional values predicted by mutation-selection balance) because they have a molecular drive advantage over an allele that is more beneficial at the organismal level. Transposable elements insert at new places in the genome where they can disrupt gene function and thereby reduce their carrier's fitness.

Zygotic drive is an unusual form of genetic conflict because it directly reduces Darwinian fitness by killing or debilitating offspring. It is favored by gene-level selection when there is competition among siblings for limiting resources. By killing or weakening noncarrier competitor siblings, the gene(s) coding for zygotic drive gain a selective advantage because their survival is increased at the expense of siblings carrying alleles that are not identical by descent—despite any fitness loss to the parents, siblings, or other parts of the genome.

Zygotic drive of the autosomes has been observed in a wide diversity of model organisms (e.g., worms, beetles, and mice) (reviewed in Burt and Trivers 2006) in which it can be efficiently detected because of the availability of numerous genetic markers. In general, an autosomal zygotic driver must have both a driver allele at one locus and a protective allele at a responder locus. In worms (*Caenorhabditis elegans*), a molecular mechanism leading to zygotic drive was recently discovered. Here a zygotic driver is coded by a pair of tightly linked genes, in which an allele at one gene (*peel-1*) produces a toxin, the driver locus, which is packaged in the sperm and transmitted to the zygote, whereas an allele at another gene (*zeel-1*) produces an antidote (the protective allele, which is expressed very early in development) that rescues only those embryos that inherit *zeel-1* (and usually also the tightly linked driver, *peel-1*) (Seidel et al. 2011). Zygotic drive on the autosomes is expected to be difficult to evolve—and therefore to be relatively rare in genomes—because it requires an improbable phenotype (i.e., a functionally coupled driver gene product and a responder gene sequence or product) and genotype (i.e., very close linkage between the loci coding for the driver and responder).

SEXUALLY ANTAGONISTIC ZYGOTIC DRIVE

Here we focus on zygotic drive coded by the X and Y (or Z and W) sex chromosomes. This phenomenon is called sexually antagonistic zygotic drive (hereafter, SA-ZD) because any gain by one sex chromosome transmitted from a heterogametic parent is at the expense of the noncarrier sex of offspring (sons or daughters) (Rice et al. 2008). Like autosomal zygotic drive, SA-ZD is favored by gene-level selection when there is sib competition for limiting resources. In addition, SA-ZD is also favored when there is a nontrivial rate of brother–sister mating and inbreeding depression. This occurs because when sisters are harmed by producing inbred

offspring from sib mating (but brothers benefit from sib mating owing to lower opportunity costs) (Haig 1999), the paternal X is selected to kill sons so that they do not fertilize their sisters, which inherit the paternal X.

Linkage to the sex chromosomes facilitates the evolution of a zygotic driver (SA-ZD) in four ways. For simplicity in the following, but without loss of generality, we will assume male heterogamety (X and Y sex chromosomes) and the terms X and Y will refer to their regions that do not recombine in males. First, all genes on the Y cosegregate across each generation, and as a consequence, the component genes coding for Y-linked SA-ZD (e.g., driver and responder genes, or polygenes coding for either trait) need not be positioned at nearby chromosomal loci—only located on the same-sex chromosome. Second, nonrecombining X and Y sex chromosomes are far more genetically diverged than homologous autosomes—because the latter are continually homogenized by recombination—making the number of potential responder loci (alleles not present on the same chromosome as the driver allele) far larger for the X and Y sex chromosomes than the autosomes. Third, there is no absolute requirement for a responder locus on a homologous chromosome because noncarrier offspring can be killed (or, more generally, harmed) when the driver gene product disrupts a sex-limited ontogenetic pathway (harming only the noncarrier sex, e.g., via epigenetic changes produced during spermatogenesis and transmitted to offspring) that is coded by any chromosome. Fourth, as mentioned above, SA-ZD is favored by gene-level selection in response to both sib competition (like autosomal zygotic drive) but also by nontrivial levels of sib–sib mating with any level of inbreeding depression.

The logic of the genetic conflict that underlies SA-ZD is identical to that of cytoplasmic genomes that are only transmitted across multiple generations via the matriline. In response to matrilineal transmission (or very low levels of patrilineal transmission in some species) (e.g., Nunes et al. 2013), mitochondria and cytoplasmically transmitted endosymbionts (like *Wolbachia* and *Spiroplasma)* have evolved to kill gametes or offspring that give rise to lineages that do not transmit them (pollen and sons) and compete for resources with the matrilineal offspring that do transmit them (reviewed in Burt and Trivers 2006). By the same logic, paternal X and Y sex chromosomes are selected to kill (or harm and make less competitive) the sex of offspring that does not reproduce them, but competes with the sex that does reproduce them. Given the widespread evolution of pollen killing in plants (coded by mitochondria in hundreds of species) (reviewed in Burt and Trivers 2006) and male killing and cytoplasmic incompatibility in animals (coded by bacterial endosymbionts in thousands of species of animals) (reviewed in Burt and Trivers 2006), it would be surprising if this same selection pressure did not lead to the widespread evolution of SA-ZD.

Collectively, the unique characteristics of sex chromosomes would be expected to cause SA-ZD to evolve via an unusually powerful evolutionary mechanism called a "green-beard effect" (Hamilton 1964; so named by Dawkins 1976) that was originally described in the context of animal behavior but later extended to molecular and cellular interactions as well (e.g., Haig 1996). A green-beard effect is a multifarious trait coded by a single gene that pleiotropically produces three distinct characteristics (or a group of tightly linked genes, each coding for a different part of the green-beard effect). First, it causes the carrier to produce a distinguishing phenotype (tag). Second, it causes the carrier to differentiate among other individuals—in the context of interactions—based on the presence or absence of the tag (tag differentiation). And third, the first two traits collectively lead to increased fitness of other individuals that express the tag (tag-directed aid). A green-beard effect is antagonistic when it increases the relative fitness of individuals carrying the gene(s) that codes for it by reducing the fitness of competitors that do not express the tag. Because green-beard effects require a complex and multifarious pleiotropy (or very tight linkage of a cluster of component genes), they have previously been presumed to be too rare in nature to be a major evolutionary force, although a few

established examples are well documented (e.g., Keller and Ross 1998, Quellar et al. 2003, Sinervo et al. 2006). However, single sex-linked genes coding for SA-ZD can easily achieve all the characteristics of a green-beard effect because (1) the tag is any sexually dimorphic trait coded by any gene in the genome, (2) the tag differentiation is any phenotype coded by one of the sex chromosomes causing fathers (or siblings) to interact differently toward sons (brothers) and daughters (sisters), and (3) the tag-directed aid/harm is any trait included in (2) that increases the fitness of the sex of offspring that carries them. For example, an X-linked mutation with male-limited expression that caused a sire to invest more in daughters at the expense of sons would lead to SA-ZD, as would a Y-linked gene causing the father to invest more in sons. Similarly, an X-linked mutation expressed in sperm producing a gene product that epigenetically silenced a dosage-sensitive gene in a male-specific ontogenetic pathway (like dosage compensation in flies) would lead to SA-ZD if the epigenetic mark persisted across generations. A fuller account of how SA-ZD simplifies the operation of green-beard effects can be found in Rice et al. (2008).

Unlike segregation distortion, which only can operate via a very limited range of phenotypes that reduce the number of noncarrier functional sperm, SA-ZD can operate through four distinct mechanisms. First, through paternal effects (especially in the context of transgenerational epigenetic influences on gene expression) that kill or harm the noncarrier sex. As described above, dead or harmed noncarrier siblings free up shared resources among siblings and thereby increase the fitness of carrier siblings. Paternal effects have been historically assumed to be sufficiently rare and/or of small effect that they can be safely ignored in genetic analyses like those for estimating heritability (e.g., paternal half-sib analysis). However, recent evidence indicates that this assumption can be mistaken (reviewed in Rice et al. 2008). For example, a recent study in mice indicated that a father's Y chromosome influences a large suite of polygenic traits in his daughters (that do not carry it) just as much as his X chromosome (which they all carry). Both X- and Y-linked paternal effects on egg-to-adult survival have also recently been documented in fruit flies (Friberg et al. 2012).

Second, sib–sib interactions that favor same-sex sibs: All Y-linked genes are identical by descent among brothers (but not with sisters) sired by the same father, as are all paternal X-linked genes among sisters (but not with brothers). As a consequence, SA-ZD is predicted to operate via brothers helping each other more than their sisters and/or harming sisters to free up more shared resources for their brothers (and vice versa for sisters interacting with each other vs. brothers). Examples of sex-specific altruism and harm (including siblicide) are common in nature (see, for review, Rice et al. 2009), so this route to SA-ZD is clearly feasible. However, there are many potential adaptive scenarios that predict sex-specific sib–sib help and harm, so none of these examples provide unequivocal evidence for SA-ZD operating via this route. As a consequence, SA-ZD operating via sib–sib interactions would be ambiguous and easily overlooked.

Third, sex-specific parental investment and/or harm: SA-ZD is predicted to operate by X- and Y-coded phenotypes that cause fathers to help one sex of offspring at the expense of the other sex. This includes killing or directly harming the noncarrier sex of offspring. Sex-specific parental investment and harm are well documented in the behavioral literature (see review of evidence in Rice et al. 2008, 2009), so this route to SA-ZD is clearly feasible. However, like the data on sex-specific sib–sib interactions, it is not clear what selective agents were responsible for building these phenotypes. As a consequence, SA-ZD operating via parent–offspring interactions would be ambiguous and easily overlooked.

Fourth, sex-specific investment by paternal grandmothers in grandchildren: Because a father inherits his X only from his mother, paternal grandmothers are related through their X chromosomes only to paternal granddaughters and not to paternal grandsons. This asymmetry is absent between maternal grandmothers and their grandchildren. As a consequence, SA-ZD

is predicted to (1) operate by grandmothers favoring their paternal granddaughters, including harming their paternal grandsons to free more shared resources, and (2) this pattern is predicted to be absent between grandmothers and their maternal grandchildren (Rice et al. 2010). Surprisingly, recent anthropological data appear to support this counterintuitive prediction in humans (Fox et al. 2010, 2011). Potential confounds, such as paternity uncertainty and genome-wide Hamiltonian relatedness, cannot explain the observed grand-maternal harm that occurs exclusively in the patriline (Fox et al. 2010, 2011; Rice et al. 2010). Paternal grandparental investment in grandoffspring is rare in nature (humans being an exception), so this route to SA-ZD is expected to have limited application.

WHY NO PRIOR EVIDENCE?

If SA-ZD is such a feasible mechanism for genetic conflict, then why has it not already been widely reported? We have already described in the above three paragraphs why SA-ZD via sib–sib, parent–offspring, and grandparent–offspring interactions would be expected to be easily confused with other causative agents, and therefore undetected. Here we focus on SA-ZD via transgenerational epigenetic effects that harm or kill the noncarrier sex. Unlike autosomal zygotic drive, SA-ZD leads to biased sex ratios, so Fisherian sex ratio selection (i.e., parents producing the rarer sex leave more descendent grand offspring) is expected to rapidly lead to repressors on the opposite sex chromosome and/or the autosomes. As a consequence, extant genes coding for SA-ZD will almost always be hidden because drive only operates episodically immediately after a de novo driver evolves or when extant but suppressed drivers temporarily escape suppression owing to new mutations or immigration of foreign drivers into a genetic background lacking the corresponding suppressors. However, this same constraint also applies to sex-linked segregation distorters and many examples of this phenomenon have been reported in the literature (Jaenike 2001). The difference with SA-ZD is that it is mediated by sex-specific mortality. Clear evidence for sex-linked segregation distortion is readily obtained (leading to detailed studies) when brood mortality is too low to account for the observed sex ratio distortion, making it relatively easy to identify this causative route to sex ratio distortions observed in nature. Brood mortality in the case of SA-ZD confounds this process with sex-specific mortality (coded anywhere in the genome) so no simple observations can unambiguously identify SA-ZD. For example, Noor and Coyne (1995) observed strong sex ratio distortion (female biased) in a laboratory stock of *Drosophila simulans* they named skew—leading them to suspect an X-linked segregation distorter. Many experiments were performed with the skew stock (and a control stock—named Florida City—with an even sex ratio) to characterize the genetics behind the sex ratio bias. However, when they checked the egg hatch rate, it was found to be elevated substantially when the sires were from the skew stock but not in the reciprocal cross with Florida City sires. When the extra mortality was applied to the rarer sex (males) there was a nearly perfect congruence with the observed sex ratio and Noor and Coyne abandoned their experiments concluding that the sex ratio bias was associated with some form of sex-specific mortality. However, the empirical pattern observed by Noor and Coyne was exactly what would be expected with SA-ZD. This example illustrates how SA-ZD could be prevalent but overlooked—even when its signature phenotype is observed (sex ratio bias associated with elevated mortality in broods), it is dismissed as mundane sex-specific mortality, i.e., as uninteresting. A few years ago we reanalyzed the skew stock studied by Noor and Coyne and found substantial—but not irrefutable—evidence that it does in fact express SA-ZD (Friberg et al. 2011).

In sum, we believe that SA-ZD is plausibly a relatively common but overlooked and unappreciated form of genetic conflict because (1) it is suppressed most of the time (like sex-linked segregation distortion) and when it is observed, it is too easily confused with sex-specific mortality (unlike sex-linked segregation distortion); (2) it can feasibly operate through a phenotype

that debilitates but does not kill competing offspring of the noncarrier sex, which makes it harder to detect than segregation distorters that always skew the frequency of offspring toward those carrying the driver; and (3) moderately strong drivers lead to only modest sex ratio distortion and are therefore hidden by sampling error. To illustrate the last point, consider a driver that was present at a frequency of 50% and killed 25% of sons (a substantial level of male mortality). In this case, the expected population sex ratio (% females) would be 0.536. Even in families in which the sire carried the driver the sex ratio would be only 0.571. Limitations on sample sizes would cause these small deviations from an even sex ratio to be hidden by sampling error or confused with weak sex-specific mortality in most empirical studies. Now that a theoretical framework has been established for SA-ZD, future cases of sex ratio distortion associated with elevated mortality of the rarer sex will hopefully be tested for the operation of SA-ZD.

GAMETIC DRIVE AND SA-ZD—DISTINCT PHENOTYPES PRODUCED BY ONE MOLECULAR MECHANISM?

So far in this article, we have treated SA-ZD as separate and distinct from sex-linked segregation distortion. However, these two forms of genetic conflict may share a common origin in the context of SA-ZD mediated via paternal transgenerational epigenetic effects. In *Drosophila melanogaster*, the autosomal segregation distorter *Sd*, and in *D. simulans* the X-linked segregation distorters *Paris* and *Winters*, all drive by modifying Y-bearing sperm in such a way that they develop improperly during spermatogenesis (reviewed in Meiklejohn and Tao 2010; Larracuente and Presgraves 2012). In *D. melanogaster*, drive via *Sd* occurs because a pericentric satellite (Rsp^s, a repetitive DNA sequence in the heterochromatin neighboring the centromere) is present on sensitive chromosomes and responds to the presence of *Sd* (by an unknown molecular mechanism) to facilitate improper chromatin remodeling during spermatogenesis. This remodeling error occurs because the driver gene (now known to be a truncated duplication of the gene *RanGAP* and renamed *Sd–RanGAP*) blocks the histone-to-protamine replacement during spermatogenesis. When the responder satellite has a low copy number of repeats (Rsp^i), chromatin remodeling occurs properly and drive is suppressed. Defective chromatin remodeling during mitosis and/or spermatogenesis is also feasibly responsible for the sperm defects seen with the two sex-linked drivers in *D. simulans* (Cazemajor et al. 2000; Tao et al. 2007; Meiklejohn and Tao 2010). We will collectively refer to such improper chromatin remodeling as ectopic epigenetic marks (ectopic-epi-marks).

Suppressors of segregation distortion via defective chromatin remodeling can act in three ways: (1) suppress gene expression at the driver locus, (2) modify the responder locus so that ectopic-epi-marks are not formed, or (3) tolerate driver-induced ectopic-epi-marks during meiosis and spermatogenesis via some compensation mechanism. In the latter case, if the driver-induced ectopic-epi-mark(s) of Y-bearing sperm were transgenerationally transmitted to the zygote (e.g., the Y is known to be imprinted in *D. melanogaster*) (Maggert and Golic 2002) they could disrupt embryonic development in at least some sons—leading to SA-ZD. For example, if transgenerational ectopic-epi-marks on Y-bearing sperm slowed the transition between a condensed sperm nucleus into a decondensed pronucleus, then mitotic checkpoints—that operate independently in the male and female pronuclei in flies—would be expected to lead to asynchronous entrance into the first mitotic division in the zygote, causing (1) permanent arrest of subsequent cell division, or (2) aneuploid mitotic products that could induce death or malformations later in development (Landmann et al. 2009). This is the same cell-cycle asymmetry in timing between male and female pronuclei that leads to embryo death during cytoplasmic incompatibility (CI) in *Drosophila* (Landmann et al. 2009), but in this case only the males would be killed (as occurs with the CI-like mortality of sons produced by some male-killing *Wolbachia*) (e.g., Riparbelli et al. 2012) because only

sons would have sperm-derived pronuclei with ectopic-epi-marks. In sum, suppressors of sex-linked segregation distortion can, in principle, convert segregation distortion into SA-ZD.

A SIMPLE MOLECULAR PATHWAY TO SA-ZD

To illustrate a potential molecular mechanism for SA-ZD via ectopic-epi-marks, again consider the phenomenon of CI caused by *Wolbachia* in flies. Here infected males produce sperm that cause embryonic mortality owing to defective chromatin remodeling of the sperm pronucleus before the first mitotic division of the zygote, but only when mated to uninfected females (Landmann et al. 2009). Like an X coding for son-killing SA-ZD via transgenerational ectopic-epi-marks, *Wolbachia* of infected sires are not transmitted to sons and must kill zygotes via modified sperm, which is accomplished via modified sperm chromatin that is not properly remodeled in *Wolbachia*-free female flies (Landmann et al. 2009). The molecular mechanisms underlying this chromatin remodeling defect are not fully resolved, but *Wolbachia*-infected sires are established to have reduced expression of the chromatin remodeling protein HIRA (Zheng et al. 2011). HIRA is important in remodeling a type of nucleosome (containing histone H3.3) that is far more common on the X compared with the Y sex chromosome. Sires that express a loss-of-function allele at the *Hira* locus produce male-biased sex ratios owing to higher early embryonic death of daughters compared with sons, presumably because X-bearing sperm carry a higher load of chromatin defects compared with Y-bearing sperm (owing to the higher frequency of HIRA-dependent nucleosomes on the X compared with the Y) (Zheng et al. 2011). Interestingly, dams that are infected with *Wolbachia* have elevated expression of HIRA in their eggs and this maternal effect is associated with complete rescue of daughters (from early embryonic death owing to sperm from HIRA-deficient sires) and restores an even brood sex ratio (Zheng et al. 2011). These HIRA phenotypes in males and females illustrate a simple pathway by which Y-linked SA-ZD could be produced in sires and suppressed via a maternal effect in dams.

SA-ZD AND HYBRID INFERTILITY

It is well established in flies that segregation distortion, especially when X and/or Y linked, has contributed importantly to the evolution of male hybrid infertility, at least in the F_2 or backcross generations (reviewed in Johnson 2010; Presgraves 2010). Like segregation distortion, SA-ZD could play an important role in the evolution of hybrid infertility and inviability during the speciation process. As described above, gene-level selection directly selects for the X to induce paternal-effect infertility in sons (to protect daughters from harmful sib mating with associated inbreeding depression), and for both the X and Y to code for paternal-effect inviability of sons and daughters, respectively (to reduce competition for shared limiting resources and to prevent sons from mating with their sisters). If SA-ZD and its suppressors evolved separately in sister species, and if such SA-ZDs were suppressed by maternal effects, then hybrid crosses in both directions would be expected to produce inviable and/or sterile offspring and contribute to postzygotic reproductive isolation in the F_1. If SA-ZDs were suppressed in the sires of each of the sister species, then the same phenotypes producing hybrid infertility and death would be expected, but in the progeny of the F_2 and backcrosses. The feasibility of SA-ZD contributing to postzygotic reproductive isolation is more fully discussed in Rice et al. (2008, 2009), as is its potential to contribute to the decay of Y and W sex chromosomes.

CONCLUSIONS

In closing we conclude that SA-ZD may be a prevalent form of genetic conflict that has the potential to have important ramifications in fundamental processes like speciation and the degeneration of Y and W sex chromosomes. It represents one of the few evolutionary phenomena that—like many cases in physics—was predicted to exist by the mathematically explicit theory alone, before any empirical evidence.

Nonetheless, SA-ZD is expected to be a largely unknown and unappreciated phenomenon that is "hidden in plain sight" because it is (1) only episodically expressed owing to repression by coevolved suppressors most of the time, (2) hidden by binomial sampling error when expressed and of weak or moderate strength, (3) confused with sex-specific viability factors when expressed at any strength, (4) confused with diverse alternative causations in the cases of sib–sib, parent–offspring, and grandparent–offspring behavioral interactions, and (5) very difficult to detect when its phenotype only reduces the competitive ability of noncarrier offspring instead of killing them. The first two factors are shared with sex-linked segregation distortion (which is well documented in nature), but the last three factors have feasibly caused this theoretically predicted form of genetic conflict to elude empirical detection when present, and consequently it would remain obscure and unappreciated even if prevalent.

ACKNOWLEDGMENTS

We thank Adam Chippindale for valuable comments on an earlier version of this review. This study is supported by grants from the Swedish Research Council and the Swedish Foundation for Strategic Research.

REFERENCES

Burt A, Trivers R. 2006. *Genes in conflict: The biology of selfish genetic elements*. Belknap Press of Harvard University Press, Cambridge, MA.

Cazemajor M, Joly D, Montchamp-Moreau C. 2000. Sex-ratio meiotic drive in *Drosophila simulans* is related to equational nondisjunction of the Y chromosome. *Genetics* **154:** 229–236.

Dawkins R. 1976. *The selfish gene*. Oxford University Press, Oxford.

Elde NC, Roach KC, Yao MC, Malik HS. 2011. Absence of positive selection on centromeric histones in *Tetrahymena* suggests unsuppressed centromere-drive in lineages lacking male meiosis. *J Mol Evol* **72:** 510–520.

Fox M, Sear R, Beise J, Ragsdale G, Voland E, Knapp LA. 2010. Grandma plays favourites: X-chromosome relatedness and sex-specific childhood mortality. *Proc R Soc B* **277:** 567–573.

Fox M, Johow J, Knapp LA. 2011. The selfish grandma gene: The roles of the X-chromosome and paternity uncertainty in the evolution of grandmothering behavior and longevity. *Int J Evol Biol* **2011:** 165919.

Friberg U, Stewart AD, Rice WR. 2011. Empirical evidence for son-killing X chromosomes and the operation of SA-zygotic drive. *PLoS ONE* **6:** e23508.

Friberg U, Stewart AD, Rice WR. 2012. X and Y chromosome linked paternal effects on a life history trait. *Biol Lett* **8:** 71–73.

Haig D. 1996. Gestational drive and the green-bearded placenta. *Proc Natl Acad Sci* **93:** 6547–6551.

Haig D. 1999. Asymmetric relations: Internal conflicts and the horror of incest. *Evol Hum Behav* **20:** 83–98.

Hamilton WD. 1964. Genetical evolution of social behaviour 2. *J Theor Biol* **7:** 17–52.

Huxley J. 1942. *Evolution: The modern synthesis*. Allen and Unwin, London.

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

Johnson NA. 2010. Hybrid incompatibility genes: Remnants of a genomic battlefield? *Trends Genet* **26:** 317–325.

Keller L, Ross KG. 1998. Selfish genes: A green beard in the red fire ant. *Nature* **394:** 573–575.

Landmann F, Orsi GA, Loppin B, Sullivan W. 2009. *Wolbachia*-mediated cytoplasmic incompatibility is associated with impaired histone deposition in the male pronucleus. *PLoS Pathog* **5:** e1000343.

Larracuente AM, Presgraves DC. 2012. The selfish segregation distorter gene complex of *Drosophila melanogaster*. *Genetics* **192:** 33–53.

Maggert KA, Golic KG. 2002. The Y chromosome of *Drosophila melanogaster* exhibits chromosome-wide imprinting. *Genetics* **3:** 1245–1258.

Meiklejohn CD, Tao Y. 2010. Genetic conflict and sex chromosome evolution. *Trends Ecol Evol* **25:** 215–223.

Noor MAF, Coyne JA. 1995. Research note. *Dros Inf Serv* **76:** 151–152.

Nunes MDS, Dolezal M, Schloetterer C. 2013. Extensive paternal mtDNA leakage in natural populations of *Drosophila melanogaster*. *Mol Ecol* **22:** 2106–2117.

Presgraves DC. 2010. The molecular evolutionary basis of species formation. *Nat Rev Genet* **11:** 175–180.

Queller DC, Ponte E, Bozzaro S, Strassmann JE. 2003. Single-gene greenbeard effects in the social amoeba, *Dictyostelium discoideum*. *Science* **299:** 105–106.

Rice WR, Gavrilets S, Friberg U. 2008. Sexually antagonistic "zygotic drive" of the sex chromosomes. *PLoS Genet* **4:** e1000313.

Rice WR, Gavrilets S, Friberg U. 2009. Sexually antagonistic chromosomal cuckoos. *Biol Lett* **5:** 686–688.

Rice WR, Gavrilets S, Friberg U. 2010. The evolution of sex-specific grandparental harm. *Proc R Soc B* **277:** 2727–2735.

Riparbelli MG, Giordano R, Ueyama M, Callaini G. 2012. *Wolbachia*-mediated male killing is associated with defective chromatin remodeling. *PLoS ONE* **7:** e30045.

Seidel HS, Ailion M, Li J, van Oudenaarden A, Rockman MV, Kruglyak L. 2011. A novel sperm-delivered toxin causes late-stage embryo lethality and transmission ratio distortion in *C. elegans*. *PLoS Biol* **9:** e1001115.

Sinervo B, Chaine A, Clobert J, Calsbeek R, Hazard L, Lancaster L, McAdam AG, Alonzo S, Corrigan G, Hochberg ME. 2006. Self-recognition, color signals, and cycles of greenbeard mutualism and altruism. *Proc Natl Acad Sci* **103:** 7372–7377.

Tao Y, Masly JP, Araripe L, Ke Y, Hartl DL. 2007. A sex-ratio meiotic drive system in *Drosophila simulans*: I. An autosomal suppressor. *PLoS Biol* **5:** e292.

Yoon SR, Choi SK, Eboreime J, Gelb BD, Calabrese P, Arnheim N. 2013. Age-dependent germline mosaicism of the most common noonan syndrome mutation shows the signature of germline selection. *Am J Hum Gene* **92:** 917–926.

Zheng Y, Ren P-P, Wang J-L, Wang Y-F. 2011. *Wolbachia*-induced cytoplasmic incompatibility is associated with decreased HIRA expression in male *Drosophila*. *PLoS ONE* **6:** e19512.