ANNUAL REVIEWS

Annual Review of Genetics

Standard Deviations: The Biological Bases of Transmission Ratio Distortion

Lila Fishman and Mariah McIntosh

Division of Biological Sciences, University of Montana, Missoula, Montana 59812, USA; email: lila.fishman@mso.umt.edu

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

Annu. Rev. Genet. 2019. 53:347–72

First published as a Review in Advance on September 10, 2019

The *Annual Review of Genetics* is online at genet.annualreviews.org

https://doi.org/10.1146/annurev-genet-112618-043905

Copyright © 2019 by Annual Reviews.
All rights reserved

ANNUAL REVIEWS CONNECT

www.annualreviews.org

- Download figures
- Navigate cited references
- Keyword search
- Explore related articles
- Share via email or social media

Keywords

segregation distortion, non-Mendelian inheritance, meiotic drive, hybrid incompatibility, inbreeding depression, selfish genetic element

Abstract

The rule of Mendelian inheritance is remarkably robust, but deviations from the equal transmission of alternative alleles at a locus [a.k.a. transmission ratio distortion (TRD)] are also commonly observed in genetic mapping populations. Such TRD reveals locus-specific selection acting at some point between the diploid heterozygous parents and progeny genotyping and therefore can provide novel insight into otherwise-hidden genetic and evolutionary processes. Most of the classic selfish genetic elements were discovered through their biasing of transmission, but many unselfish evolutionary and developmental processes can also generate TRD. In this review, we describe methodologies for detecting TRD in mapping populations, detail the arenas and genetic interactions that shape TRD during plant and animal reproduction, and summarize patterns of TRD from across the genetic mapping literature. Finally, we point to new experimental approaches that can accelerate both detection of TRD and characterization of the underlying genetic mechanisms.

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

INTRODUCTION

The random transmission of alternative alleles at a diploid locus to gametes and progeny, codified as Mendel's law of equal segregation, is a cornerstone of genetics and evolutionary biology. Equal segregation is generally favored by natural selection, as the "parliament of genes" (88, p. 4543) opposes transmission bias at any given locus (38). Thus, the machinery of meiosis and gametogenesis has evolved to maintain Mendelian inheritance, and Mendel's first law generally holds true. However, as new technologies provide unprecedented power to examine genome-wide patterns of allelic transmission, it is increasingly clear that biologically based deviations from Mendelian inheritance, as scored by progeny counts, are common. Such deviations, broadly termed transmission ratio distortion (TRD), can result from a variety of selective processes during meiosis, gametogenesis, fertilization, and offspring development. TRD is a nuisance in genetic mapping studies, as it can skew intermarker distances (93) and, when severe enough to reduce the effective sample size of informative genotypes (148), bias quantitative trait locus (QTL) estimation. However, as locus-specific indicators of selection, mapped TRD loci (TRDLs) also provide invaluable insight into genetic and evolutionary mechanisms of individual fitness variation, population divergence, and speciation.

Our goal is to provide (*a*) an overview of the arenas for selection where TRD can be generated, (*b*) a summary of patterns of marker TRD from the genetic mapping literature, and (*c*) practical tips for experimentally diagnosing the mechanistic basis of TRD, with particular reference to seed plants and vertebrates. We focus on the empirical phenomenon of TRD, which can arise from diverse underlying processes, rather than attempting an exhaustive review of any one causal mechanism. Other recent reviews cover diverse selfish elements (20, 66, 95) and mechanisms of meiotic drive in the broad sense (91), as well as gamete killers (15) and female meiotic drive by chromosomes (82, 83). Although TRD in hybrids is often casually referred to as "drive," implying a selfish evolutionary history for distorted loci, we emphasize that selfish meiotic drive within a species is only one of many sources of non-Mendelian transmission in both intra- and interspecific contexts. We use the term TRD to describe the phenomenon of non-Mendelian genotypic or allelic ratios in gametes or offspring of heterozygotes. We use specific descriptions of the proximate causes of TRD (e.g., early zygote death, pollen competition) where known or hypothesized, while limiting the terms drive or meiotic drive to those cases in which the ultimate evolutionary mechanisms are known to be selfish within species (i.e., due to natural selection below the level of the individual).

MAPPING AND MEASURING TRANSMISSION RATIO DISTORTION

Detecting TRD depends on informative polymorphism, as well as well-defined null expectations. That is, understanding whether progeny genotypes deviate from Mendelian expectations requires prior knowledge of the parental genotypes and a model of expected transmission. Depending on the experimental context, this can range from the full genome sequence of two inbred lines and their F_1 hybrid from which all F_2 progeny are derived, to multigeneration pedigrees of genotyped outbred individuals, to statistical estimates of allele frequencies in a population. New genomic technologies and analytical approaches make analysis of TRD through outbred pedigrees and populations increasingly feasible (65, 92). Indeed, genomic selection component analysis (27, 109) uses locus-specific deviations from Mendelian transmission (i.e., TRD) across generations to infer the magnitude and mechanisms of natural selection in wild populations (see the sidebar titled Selection Component Analysis). Intermediate between pedigree and line cross approaches is the collaborative cross (reviewed in 34), in which many genetic lineages serve as founders of a large segregating population, often maintained through multiple generations to maximize

SELECTION COMPONENT ANALYSIS

Just as locus-specific deviations from Mendelian transmission can reveal meiotic, gametic, or zygotic selection in mapping populations, genomic selection component analysis (gSCA) uses shifts in population or cohort allele frequencies to estimate stage-specific fitness effects. gSCA is derived from single-locus selection component analysis (27) but leverages next-generation sequencing and the (generally) low linkage disequilibrium in outbred wild populations to identify single-nucleotide polymorphisms under selection. Especially in taxa (such as plants or invertebrates) in which large numbers of individuals and their progeny can be readily collected, gSCA can efficiently scan for differential fitness by comparing allele frequencies within generations (e.g., in germinant versus adult samples to estimate viability selection) and across generations (e.g., by comparing many mother–progeny sets). gSCA can utilize even low-coverage genome sequences, with appropriate accounting for genotyping uncertainty (46, 109). As it becomes increasingly economical to sequence large numbers of individuals, gSCA is likely to become a widely applied tool for understanding the genome-wide effects of natural selection (including gametic and sexual selection) in the wild. However, as with TRD in mapping populations, complementary measures of individual phenotypes and fitness (or experimental manipulation) may be necessary to pin down the specific targets or modes of selection.

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

recombination. For example, substantial TRD in a mouse collaborative cross contributed to the recent discovery of a novel maternal drive element (R2d2; 36) that is also selfishly evolving in wild populations (37). Similarly, shifts in allele frequency across generations of the wheat multiparent advanced generation intercross (MAGIC) collaborative cross identified loci associated with selection on flowering time (142). However, for simplicity, and because they are by far the most common context for the detection of TRD currently, we focus here on genetic mapping populations derived from controlled crosses among a small number of parents. The mechanisms and experimental considerations discussed here also apply to more complex crosses and pedigrees (with additional complexities).

The simplest context for detection of TRD is a backcross hybrid population involving hermaphroditic inbred lines; the F_1 is expected to transmit the alternative parental alleles at any F_1-heterozygous locus in equal frequencies (50:50). If the F_1 is the male parent (and conversely, if it is female), TRD is possible only through male function plus zygotic selection among backcross progeny prior to genotyping (**Figure 1**). In an F_2 inbred line intercross mapping population, distortion is possible simultaneously via male and female function as well as zygotic selection. Thus, TRD at autosomal loci cannot be assigned to male or female function in inbred F_2 designs without additional phenotypic/fitness evidence; however, F_2 hybrids may allow statistical discrimination between gametic and zygotic selection. Similar rules apply to outbred crosses (e.g., hybrids between mammal species) in which only parent-diagnostic alleles are tracked. In four-parent or three-parent F_2 crosses, it may be possible to simultaneously and separately track male- and female-specific transmission patterns for a given region using diagnostic polymorphisms (90), but this approach has not yet been widely applied. Advanced-generation hybrids based on backcross and F_2 line crosses, such as recombinant inbred lines (RILs) or nearly isogenic lines or introgression lines (NILs), have greater opportunities for zygotic selection over multiple generations, which can complicate inference. However, RILs and NILs also provide increased power for analyses of TRD caused by epistatic interactions among loci (112).

The first step in evaluating the biological basis of TRD in a mapping population is to eliminate loci distorted for nonbiological reasons, which generally requires evaluation in the context of linked loci. The best practices for linkage mapping in R/qtl (16), JoinMap (145), and other genetic mapping programs include identifying and removing those markers distorted owing to

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

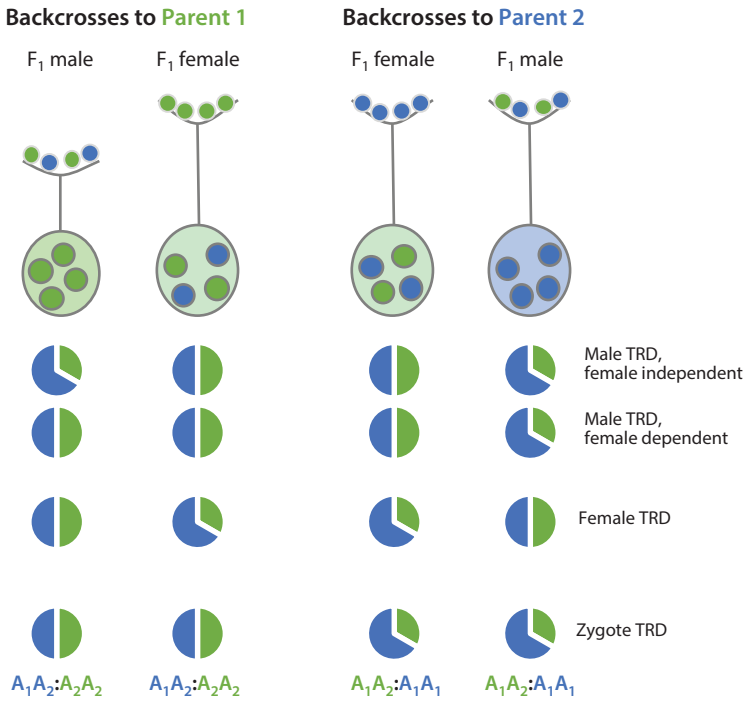

Figure 1

Patterns of male-specific, female-specific, and zygote-specific transmission expected in reciprocal backcrosses, shown for a plant cross with one small-flowered parent to illustrate asymmetry in male–male competition. If the initial F_1 hybrid is made reciprocally (producing eight possible crosses; 127), it is further possible to detect cytoplasmic and other parent-of-origin effects on meiotic and gametic transmission. Distortion in any one cross is not generally diagnostic of the stage/mechanism of TRD, but the comparative patterns shown have been useful in isolating the selective arena of TRD in several systems (39, 43, 76, 127). Figure adapted from Reference 39. Abbreviation: TRD, transmission ratio distortion.

nonbiological processes (bad markers). Biological TRD should decrease monotonically with genetic distance from the causal locus, whereas nonbiological TRD tends to be idiosyncratic to a given bad marker. In data sets with high densities of codominant markers, distinguishing between these alternatives is relatively straightforward. For example, in JoinMap, a χ^2 test statistic of observed genotype counts versus the Mendelian expectation (for a given marker class) is automatically calculated and significant deviations are flagged. This screen for bad markers can be done prior to mapping but is most useful following an initial round of marker ordering within linkage groups (or chromosomes if a physical map is available) but preceding refinement of map orders. Because biologically based TRD is proportional to genetic distance from a causal locus, linkage relationships are highly informative even when TRD is severe (149). For example, we were able to linkage map through a meiotic drive locus causing nearly 100% bias against one parental allele (i.e., 0:1:1 versus 1:2:1 segregation), despite a sparse map of mostly dominant markers (40). Even if an individual marker linked to an extreme distorting locus becomes completely noninformative and nonmappable (e.g., 100% heterozygotes in a backcross population), flanking markers will reflect both underlying linkage and monotonically decreasing TRD. Thus, assuming dense sampling and due diligence during linkage map construction itself, there may be little reason to censor highly distorted markers prior to mapping. If they are biologically distorted, they will be

at the heart of TRDLs; if they are not, they should be flagged as bad markers due to the nonlinear linkage relationships generated by incorrect individual genotypes.

On a cautionary note, however, genotyping biases could also conceivably generate TRD local to a particular genomic region, mimicking biological signal. With next-generation (e.g., Illumina short-read) sequencing, heterozygotes may be undercalled and nonreference homozygotes may be rendered as missing data if reads are mapped to a reference genome more closely related to one parental genotype (13). In regions of elevated divergence (e.g., inversions or regions of historic introgression), consistent bias across linked markers could theoretically mimic the pattern of distortion expected from biological mechanisms, especially when high missing data make both patterns noisy. Reference bias can be minimized with additional genotyping precautions, such as generating a pseudoreference based on either parental or F_1 genotypes (133), restricting genotype calling to relatively conserved (i.e., genic) regions, or dropping loci with more than a handful of missing individual genotypes. Because next-generation genotyping approaches generate vastly more markers than are necessary for resolution in moderately sized QTLs or linkage mapping populations, the last option often comes with little cost in terms of mapping power.

Assuming that uniquely distorted bad markers (and those with high counts of missing genotypes) have been removed during the iterative mapping process, the next step is to identify and characterize any TRDLs. Recently, researchers have developed Bayesian approaches that accommodate the mapping of TRDLs even in complex crossing designs and may also allow for deconvolution of linked TRDLs in dense maps (24). However, direct plotting and assessment of χ^2 test statistics or allele/genotype frequencies are common and effective in F_2 and backcross hybrid populations. In either case, however, determining the correct significance threshold to use in calling TRDLs is not straightforward. Some researchers use a full Bonferroni correction for multiple tests across the total number of markers when evaluating TRD χ^2 statistics (23, 49); however, because linked markers are not independent, such a correction is quite conservative (5, 40). For example, Gagnaire et al. (49) used a corrected threshold of $\alpha = 0.000017$ ($N = 102$ backcross individuals, ~3,000 markers), which can only flag 70:30 distortion as significant (versus ~60:40 at $\alpha = 0.05$). However, statistical conservatism may be wise, as that study nonetheless detected 27 distinct TRDLs, with at least one distorted region found on 19 of the 40 chromosomes! The appropriate threshold for a given study will depend on whether researchers are more concerned with false positives or false negatives, noting that false-positive TRDLs due to chance sampling (as opposed to stray bad markers) will be supported by flanking distortion due to the inherent nonindependence of linked markers. Controlling for the number of chromosome arms might be a reasonable middle path. Overall, large mapping populations (>300) should be used wherever detecting and estimating locus-specific TRD is an explicit research goal; low sample size increases the risk of overestimating TRDL effects above a given statistical threshold, as with QTL mapping of phenotypes (4).

In F_2 populations or multiple backcross populations, it may be possible to determine whether a TRDL is gametic or zygotic in action either by estimating additive and dominance effects in a Bayesian model (24) or by testing (with χ^2 tests) whether genotype frequencies are consistent with the (distorted) allele frequencies. When TRD is strong (and samples sizes are large), F_2 populations alone may reveal a clear pattern. For example, strong heterozygote excess with symmetrical homozygote deficits (e.g., 1:3:1 with large sample size) suggests a zygotic mechanism for TRD (114). Similarly, female meiotic drive in *Mimulus* was first detected in an interspecific F_2 population as a region of 0:1:1 segregation on one linkage group (40). The latter pattern strongly suggested meiotic or gametic selection, as the postfertilization (zygotic) loss of one homozygous progeny class predicts a 0:2:1 genotype ratio, whereas loss of one gamete class via one parent predicts the observed 0:1:1. However, linkage among multiple distorting loci and more complex

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

genetic bases may often make it difficult to statistically distinguish gametic from zygotic TRD in inbred line–cross F_2 populations. Thus, interpreting patterns of TRD initially detected in a single set of hybrids often requires isolating male-, female-, and zygote-specific distortion from multiple distinct crosses (**Figure 1**) combined with molecular, cytogenetic, and/or phenotypic tests of mechanism. This approach has been a powerful tool for understanding selfish evolution and hybrid incompatibility in *Mimulus* (monkeyflower) (39, 43, 45, 76) and *Oryza* (rice) (127). An inspirational model for such stepwise dissection of TRDLs is the classic abnormal chromosome 10 (*Ab10*) knob neocentromeric drive system in maize (*Zea mays*), in which Marcus Rhoades ruled out every alternative (including gravity!) before reaching the radical conclusion that female meiosis itself could be non-Mendelian (reviewed in 11).

MECHANISMS OF TRANSMISSION RATIO DISTORTION

Although fascinating reproductive phenomena generate TRD in fungi (58, 64, 117) and mosses (105), we focus here on causes of TRD in experimental mapping populations with a dominant diploid life stage and separate male and female meiosis and gametogenesis (i.e., animals and vascular plants). In the section that follows, we divide sources of TRD into those acting during meiosis (selection among chromosomes), from gametogenesis to fertilization (selection among haploid gametes), and during early zygote development (selection among diploid progeny) (**Table 1**, **Figure 2**). The phase in the life cycle in which selection occurs can affect both the pattern of distortion (e.g., allelic versus genotypic TRD, male-specific versus female-specific versus gender-neutral TRD) and the associated phenotypic effects (e.g., reduced male fertility with some but not all forms of gametic TRD). Thus, although isolating the stage (and/or sex) at which TRD occurs is rarely enough to pinpoint a biological cause, it is often the first and most accessible clue about

Table 1 Potential mechanisms of distortion

Stage	Mechanism	Description
Meiotic	Centromeric	Chromosomal competition during meiosis I of asymmetric (generally female in plants and animals) meiosis
	Neocentromeric	Chromosomal competition during meiosis II of asymmetric (generally female in plants and animals) meiosis
Gametic	Egg competition	Ovules/eggs could compete for resources, resulting in differential survival prior to fertilization (but this is likely rare)
	Sperm and pollen competition	A race to fertilization among haploid male gametes/gametophytes, or differential fertilization success depending on female or egg genotype
	Sperm killers (male meiotic drive) or egg killers	The gene products of one gamete haplotype selfishly kill or disable noncarrier gametes; distinct from simple competition
	Haploid-acting incompatibilities (male, female, or both)	Negative interactions among alleles within recombinant gametes or between diploid tissues and haploid gametic genotypes; distinct from gamete-killing if the phenotype is unique to hybrids and not selfish
Zygotic	Inbreeding depression	Selection against seeds/embryos homozygous for deleterious alleles; may depend on maternal resources
	Inadvertent selection	External selection (e.g., via germination or growth conditions) resulting in skewed genotypes
	Diploid-acting incompatibilities, including nuclear–nuclear and nuclear–other epistasis	Multilocus interactions causing selection against particular genotypic combinations in offspring; also includes interactions between diploid nuclear embryo genotype and organellar genotype, triploid endosperm genotype, and maternal genotype

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

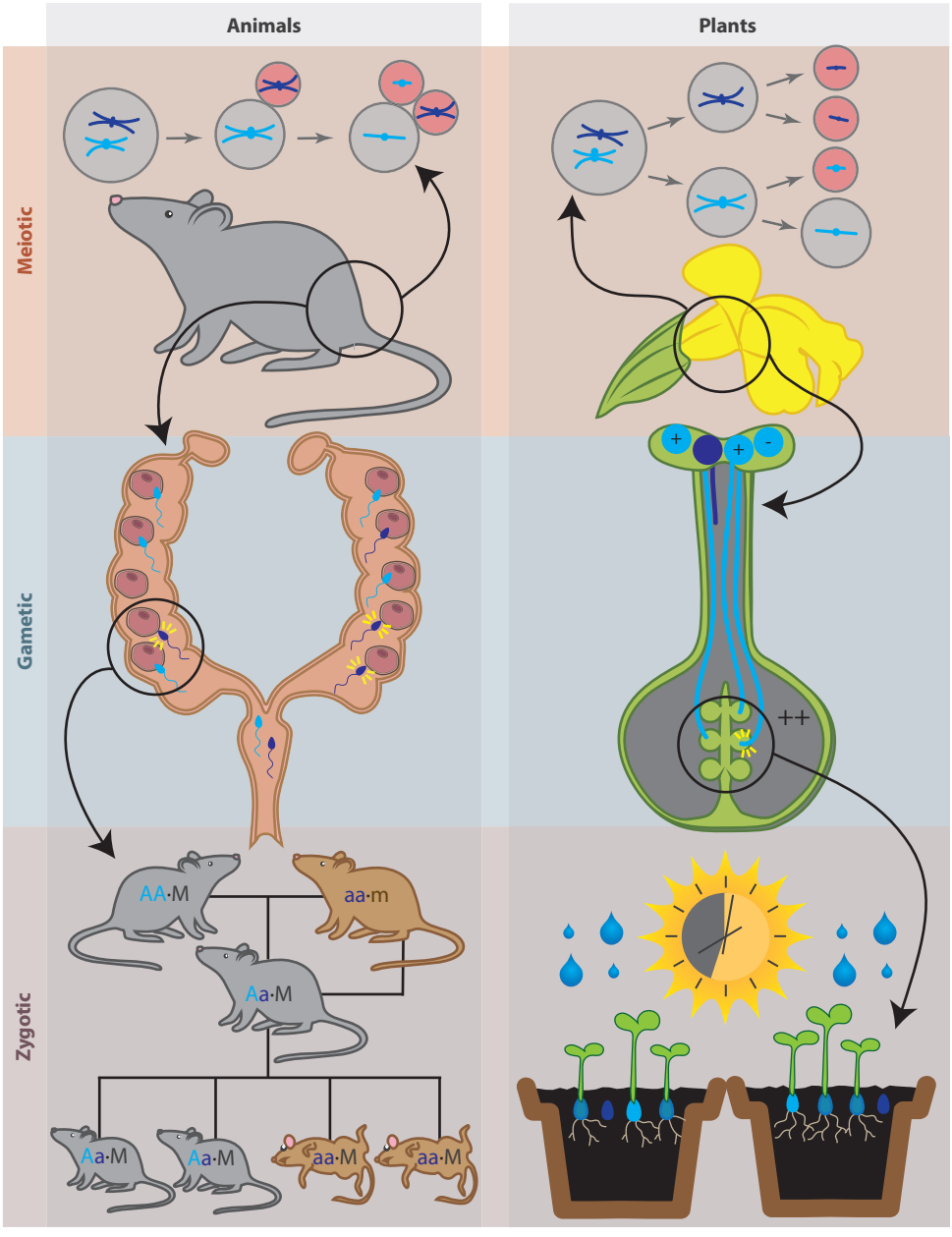

Figure 2

Arenas for selection during reproduction and mechanisms of transmission ratio distortion, illustrated for an animal [*Mus musculus* (mouse)] and a plant [*Mimulus guttatus* (yellow monkeyflower)]. Mechanisms shown include chromosomal drive at the meiotic stage for both taxa, preferential fertilization (for animals) and pollen competition (for plants) at the gametic stage, and asymmetric hybrid incompatibility (for animals) and environmental selection during germination (for plants) at the zygotic stage. The mechanisms illustrated are a subset of the complete set of mechanisms listed in **Table 1**.

the underlying mechanism. In addition to reviewing the major mechanisms that can contribute to TRD at each stage, we highlight notable empirical examples and outline theoretical predictions to guide investigations.

Meiotic Transmission Ratio Distortion

Female meiosis in most plants and animals is defined by asymmetry (120)—only one of the four haploid products of meiotic division goes on to become the oocyte (or, in plants, the eight-celled megagametophyte containing the egg cells). This asymmetry of cell fate creates a potential arena for selection, as any chromosomal variant that can preferentially segregate to the egg pole gains a transmission advantage. What kinds of loci can drive through female meiosis? Only structural variants can alter the physical outcome of meiotic divisions; genes may enhance or otherwise interact with driving structural variants, but a gene alone cannot drive through female meiosis. Centromeres, the chromosomal sites of kinetochore formation and spindle attachment, have the greatest opportunity for and most to gain from female meiotic drive (100). Genetically distinct centromeres pair at meiosis I; thus, a driving variant can achieve 100% transmission if the outcome of female meiosis is completely skewed (98). Furthermore, even slight biases in meiotic segregation can result in a transmission advantage with few costs, as taking advantage of the underlying asymmetry of female meiosis need not cause any direct reduction in female fitness. Pervasive female meiotic drive may explain the dramatic variability of centromeric DNA repeats across plants and animals, as well as the paradoxically rapid evolution of centromeric histones and other kinetochore proteins (60, 82, 99). Neocentromeric knobs and telomeres, which generally recombine with centromeres and can thus be heterozygous in sister chromatids, can similarly compete at meiosis II by manipulating segregation via mechanisms outside the normal kinetochore machinery (32, 33). By affecting centromere features, chromosomal rearrangements (particularly Robertsonian fusions/fissions in mammals) may also drive through meiosis (26). In fact, lineage-specific biases in which structural variants are favored may explain the strikingly nonrandom distribution of acrocentric- and metacentric-dominant karyotypes in mammals (119).

Chromosomal drive through female meiosis underlies several cases of female-specific, prezygotic, TRD in both animals and plants. In mouse, in which the products of meiosis I are accessible to direct study, recent work reveals the molecular mechanisms of centromeric drive: Strong centromeres recruit larger kinetochores (26, 69) and drive by taking advantage of underlying (and genetically controlled) spindle asymmetry (1). This elegant work provides a mechanistic explanation for non-Mendelian segregation by Robertsonian fusions/fissions and other chromosomal variants in mammals, as well as by larger centromeric DNA arrays. Also in mouse, the *R2d2* copy number variant is an intriguingly widespread selfish element exhibiting overtransmission in heterozygous females (37), which is consistent with chromosomal drive (36). However, the dependence of *R2d2* on unlinked enhancers and the association of TRD with reduced female fertility in heterozygotes (36) are also consistent with postmeiotic mechanisms, such as early embryo loss or nonrandom fertilization (114). A clear functional test for centromeric meiotic drive in *R2d2* and mammalian TRD systems may be enabled by the recent discovery of cellular signatures of microtubule instability that predict the direction of centromeric drive in mouse (2).

In plants, model neocentromeric and centromeric female meiotic drive systems were discovered as TRD in experimental hybrids and have also been studied in wild populations. The best-characterized neocentromeric drive system, *Ab10* knob in maize, was discovered nearly 50 years ago as TRD of a visible marker (kernel color) in controlled crosses (reviewed in 11). *Ab10* is a structural variant of maize chromosome 10 containing a heterochromatic knob of repetitive DNA, as well as a cluster of kinesin genes (33) that enable the *Ab10* knob to race to the outer poles

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

at meiosis II (61) and promote drive by knobs on other chromosomes (17). *Ab10* is widespread at low frequency across diverse maize landraces (73), and recent empirical and modeling work suggests that fitness costs balance its ~65:35 meiotic transmission advantage and maintain the polymorphism (55, 63). The driving *D* chromosomal variant in the yellow monkeyflower, *Mimulus guttatus*, has the properties of a functional (and selfish) centromere. *D* exhibits nearly 100% transmission—only via female meiosis—in interspecific hybrids (45) and contains massive arrays of centromere-specific DNA repeats (42). Within *M. guttatus*, *D* drives relatively weakly (~60:40) against conspecific alternatives and is maintained at intermediate frequency by homozygous fitness costs that balance its transmission advantages in the female meioses of heterozygotes (41). Both *M. guttatus* (126) and maize populations are notable for high levels of structural and sequence diversity, suggesting that balanced polymorphism for female meiotic drivers may be a common feature of plant (and potentially animal) populations with large effective population sizes.

Centromeric and neocentromeric drive systems in both mammals and flowering plants indicate that female meiosis is indeed a widespread arena for natural selection among chromosomes (reviewed in 131). When might we expect female meiotic drive to cause TRD in mapping populations? True meiotic drive is possible when meiosis is asymmetric (i.e., female meiosis in most plants and animals) and must involve structural divergence that can plausibly influence spindle–chromosome interactions to bias segregation. Centromeres, as well as chromosomal rearrangements that shift centromere size and position, are obvious candidates. However, not all TRD mapping to a centromeric region or rearrangement necessarily implicates drive by centromeres; low recombination in centromeric regions may cause genic loci to have physically broad effects on transmission. In addition, even slight differences in centromeric transmission via female meiosis (i.e., those too small to detect in reasonably sized mapping populations) will rapidly fix selfish chromosomes if there are no associated costs. Thus, chromosomal drivers found segregating within populations (like the maize and *Mimulus* examples above) may generally be balanced by linked reproductive costs, particularly recessive ones (41, 55). Because substantial (recessive) costs are necessary to prevent fixation of a meiotic driver and promote the evolution of suppressors, distortion in interspecific hybrids may reveal centromeric drive that is cryptic within species due to fixation rather than suppression. Finally, meiotic drive within species requires both opportunities for conflict (i.e., heterozygosity) and large effective population sizes; therefore, we do not expect meiotic drivers and similar selfish elements to spread in highly selfing plant taxa (19). Mechanistic investigations of female-specific TRD in existing and new systems will be key to understanding more broadly the prevalence and evolutionary effects of female meiotic drive.

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

Gametic Transmission Ratio Distortion

Just as femaleness in both plants and animals is defined by meiotic asymmetry (resulting in one large and precious egg), maleness is generally associated with the production of vast numbers of relatively small gametes (sperm) or gametophytes (pollen). Thus, competition for fertilization is particularly acute among male gametes and is both a major arena for selection in nature (108) and a likely source of TRD in mapping populations. Multiple distinct evolutionary phenomena may cause a pattern of gametic stage TRD, including selfish gamete killers (15), gamete competition and/or differential fertilization success, and haploid hybrid incompatibilities, affecting intrinsic gamete viability. The first two mechanisms apply primarily to male function. Several prezygotic distorter loci with joint effects on male and female function have been reported (51, 77, 78, 129), but the only one of these to be genetically dissected revealed a complex of genes with separate male and female effects (79). Therefore, we focus primarily on male-specific (and male–female interaction) mechanisms of gametic competition.

Gamete killers. The classic meiotic drive systems in animals, including *t*-haplotype in mouse and *Segregation Distorter* in *Drosophila*, are actually gamete killers that act during spermatogenesis rather than meiosis (15, 95). In gamete-killer systems, sperm carrying the nondriving haplotype are poisoned or otherwise inactivated in heterozygotes, whereas brother sperm (from the same male) carrying the driving allele remain functional. For example, in the *t*-haplotype system in mouse, wild-type and *t*-sperm are produced in equal numbers by male wild-type/*t*-heterozygotes, but wild-type sperm fail to fertilize due to flagellar dysfunction caused by the *t*-toxin (reviewed in 94). Importantly, gamete-killer systems generally involve multiple linked genes within chromosomal inversions that prevent recombination (in heterozygotes) between killer and responder genes, plus additional linked enhancer loci (15; reviewed in 84, 91). Because they involve active disabling of half of a heterozygous male's sperm, and often have linked deleterious effects when homozygous (e.g., *t* is lethal when homozygous), these well-known gamete killers generally persist as low-frequency polymorphisms within species. Recent theoretical and empirical work suggests that gamete killers should be less common in taxa with polyandry (because it shifts competition from among a single male's sperm to among sperm from many males) (102, 103) and may be mitigated by female preference for compatible mates (101).

Sex-ratio distorters are an important subcategory of gamete killers. Y-bearing sperm (generally) are targeted and disabled by gene products encoded on the X chromosome, skewing progeny sex ratios toward higher female frequencies (59, 70, 107). Sex-ratio distorters were among the first selfish genetic elements identified, in part due to the relative ease of measuring sex ratios prior to the development of genetic markers. However, such distorters appear to be widespread within the model animal taxa (i.e., dipterans and rodents) in which genetic mapping has been extensive (59), and are even found in the few flowering plants with sex chromosomes (141). As with autosomal gamete killers in inversions, suppressed recombination between heteromorphic sex chromosomes (and inversions on sex chromosomes) can facilitate the strong linkage between poison and antidote alleles necessary for nonsuicidal killing of sensitive responders. Because their costs can be substantial, sex-ratio distorter systems may often be maintained as intraspecific polymorphisms or promote the evolution of unlinked (e.g., autosomal) suppressors that make them ephemeral and cryptic within species over the longer term. The latter coevolutionary dynamics have been proposed as a major cause of rapid divergence between species and the evolution of hybrid incompatibilities (48, 67). However, the aspects of sex chromosomes that promote the evolution and detection of sex-linked gamete killers (e.g., low recombination) also make dissecting the underlying loci and assessing their population genetic histories particularly challenging.

Although they have been studied primarily in genetic model systems such as mice and *Drosophila*, gamete-killer systems are likely to be widespread (and causes of TRD) in other animals with similar population biology (i.e., large effective population sizes, low to moderate polyandry). There are few analogous systems known in plants (with the exception of a few female-specific gamete killers in rice that likely represent gametophytic hybrid incompatibilities without a history of selfish evolution; reviewed in 44). One reason may be the higher incidence of self-fertilization in plants. Selfish gamete killers should not spread in inbreeding plants (including model systems such as domesticated rice or *Arabidopsis thaliana*), as the nonindependence of male and female fitness in selfers reduces intergenomic and sexual conflict, and routine inbreeding limits the spread of selfish elements (19). However, the dearth of polymorphic pollen-killer systems even in outbred plants may also reflect the prevalence of multiple mating in most outbred flowering plant species (118). Like polyandry in animals, routine delivery of mixed pollen loads (by pollinators or wind) enlarges the arena for gamete competition, reducing any benefit of killing your own brother pollen grains. Finally, transcript sharing in animal sperm (versus substantial haploid gene expression in pollen, see below) may provide a greater opportunity for poisoning of meiosis mates while also reducing

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

opportunities for direct haploid-phase competition (reviewed in 72). Thus, although the paucity of selfish pollen-killer systems in outbred plants versus animals may just be historical accident, it may reflect the underlying biology of these groups.

Pollen and sperm competition. While a pollen grain may have little to gain from killing brothers within the same anther, and even a lot to lose if pollen fertility is important for pollinator attraction (130), it may have much to gain from competitive ability after dispersal and pollination. In addition to experiencing strong competition to fertilize a relatively small number of ovules (9, 111), flowering plant pollen grains express a large proportion (up to 50%) of their recombinant haploid genomes (reviewed in 72). Thus, Haldane's assertion that "a higher plant is at the mercy of its pollen grains" (54, p. 67) was developmentally prescient—a haploid-expressed allele in pollen has both a motive and the means to gain fitness by increasing pollen tube growth rates, even at some expense to diploid fitness (68). Thus, in outcrossers, pollen-expressed genes may be under constant selection to enhance pollen performance, whereas in selfers we expect relaxation of such sexual selection (as well as purifying selection) (14, 104). In addition, pollen performance often depends on interactions with the female reproductive tissue because the energetic demands of pollen tube growth exceed pollen resources and species-specific signals between pollen and ovule are necessary for successful fertilization (reviewed in 62, 138). In the latter case, intraspecific coevolution between style- and pollen-expressed genes may, in hybrids, result in a breakdown of communication between some pollen genotypes and recipient styles, genotype-specific failure to fertilize, and TRD (113).

Only a few mechanistic studies have distinguished plant TRD via male gamete performance from TRD via other sources. One notable exception involves the phenomenon of unilateral incompatibility, which occurs in crosses between gametophytic self-incompatible (male) and self-compatible (female) plant taxa and is common in Solanaceae (reviewed in 6). Unilateral incompatibility results in stylar rejection of pollen grains with mismatched genotypes and thus can generate pollen-specific style-dependent TRD in mapping populations with hybrid male parents, as well as conspecific pollen precedence (CPP) (57, 121). In such systems, TRD should map to the intraspecific self-incompatibility loci, and this has been demonstrated in several cases (reviewed in 113). Pistil-mediated male-specific TRD (female-dependent selection among pollen grains) may also be common within self-compatible plant lineages. In wind-pollinated maize, for example, multiple independent gametophyte factors (*ga* alleles) arrest pollen tube growth if the pollen genotype does not match that of the style, and thus act as selfish elements within species and as crossing barriers between maize and its ancestor, teosinte (75). The stylar environment may also select among pollen genotypes more quantitatively. For example, the outcrossing yellow monkeyflower, *M. guttatus*, shows near-complete CPP compared with the closely related selfer *Mimulus nasutus* in mixed pollinations of *M. guttatus* styles (35), despite high cross-fertility in pure crosses. This CPP appears highly polygenic; more than eight TRDLs identified in F_2 hybrids of these species exhibited significant style-dependent male-specific TRD in reciprocal backcrosses isolating male and female function, with many exhibiting *M. guttatus* excess greater than 60:40 (39). Marked directional CPP is consistent with long-term relaxation of male-male competition in the selfing species (104), resulting in *M. nasutus* pollen genotypes with reduced competitive ability on the *M. guttatus* stylar background. Further investigations of male-specific TRD in intra- and interspecific hybrids should provide insight into the prevalence of selection on haploid pollen as both a cause of TRD and a force in plant evolution.

Once sperm arrives at the egg, there are further opportunities for selection via gamete interactions prior to successful fertilization. For example, in some externally fertilizing marine taxa, conflict between male and female interest drives rapid evolution of gamete recognition proteins

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

(81, 89). In turn, divergence in recognition proteins contributes to barriers between populations and species. Direct interactions between male and female gametes likely contribute to patterns of TRD in mapping populations of mass-spawning taxa, but less is known about such interactions in internal fertilizers such as mammals and flowering plants. However, it has been recently argued that genotypic matching of gametes contributes to patterns of TRD in mouse hybrid populations (e.g., 114).

Gamete-expressed hybrid incompatibilities. Finally, gametic TRD can derive from hybrid incompatibilities between a gamete (or gametophyte) and the diploid (F_1) parent that produces it. Although sometimes termed gamete-killer systems, such hybrid incompatibilities need not evolve via selfish gamete-killing within a species (reviewed in 44, 139). Instead, they may simply represent mismatch between diploid (parental) and haploid (gamete) gene products that must jointly function during hybrid gamete development. Gametophyte–sporophyte hybrid incompatibilities may be particularly common in seed plants (reviewed in 44), in which both the pollen and megagametophyte (ovule) are multicellular entities that express their own haploid genomes but develop within a genetically distinct diploid individual. Unfortunately, distinguishing such interactions from selfish gamete-killing (death of haploid pollen genotypes in the presence of a killer allele in brother pollen grains), pollen competition (style dependent or not), and early postzygotic incompatibilities from patterns of progeny TRD alone is difficult. Fitness measures may help; both selfish pollen-killing and hybrid gamete–parent incompatibilities should be accompanied by reduced pollen viability, whereas early postzygotic incompatibilities should involve seed viability, and straightforward gamete competition should not entail loss of either gametes or zygotes. Nevertheless, even with fitness correlates, fine-scale genetic dissection of both TRD and hybrid infertility may be necessary to make (or break) a mechanistic connection between them. For example, a major male-specific TRD locus on linkage group 6 in *M. nasutus* × *M. guttatus* hybrids (39) is genetically coincident with the *M. guttatus* hybrid male sterility locus *hms1* (140). However, recent fine-mapping reveals that hybrid TRD at *hms1* is independent of the gametophyte–sporophyte incompatibility causing pollen inviability (as it does not vary with the genotype at the interacting *hms2* locus) and also does not appear to reflect a history of TRD via selfish pollen-killing within *M. guttatus* (76). Like similar gamete-killer systems in rice (79), this complexity is evolutionarily fascinating but challenging to unpack experimentally. Thus, as in recent reviews of hybrid incompatibility (44, 139), we advocate for careful genetic dissection and (ideally) population genomics analyses prior to the conclusion that gametic death or TRD in hybrids has its evolutionary origins in selfish within-population gamete-killing. Many such loci may indeed have selfish histories, but selfishness is a testable population genomics hypothesis (22) rather than an inference that can be made from the hybrid TRD or infertility alone.

Zygotic Transmission Ratio Distortion

Zygotic TRD occurs through the nonrandom loss of diploid zygotes between fertilization and genotyping and thus has many potential sources. Importantly, because zygotic TRD involves differential death, it may often be associated with measurable reductions in maternal fertility or offspring mortality. Such fitness effects can provide important clues about the mechanism of TRD (and vice versa). However, depending on whether selection occurs within the mother (i.e., during seed or embryo development), early in juvenile development (e.g., at germination), or during a later juvenile stage, detectable mortality may not be directly proportional to the degree of TRD. In particular, situations in which mothers mature only a subset of fertilized eggs may allow for numerical replacement of lost offspring with others carrying more fit genotypes. Such

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

reproductive compensation is well documented for both animals and plants (52) and can buffer maternal fertility even when early-acting loss of zygotes causes TRD.

In this section, we describe three major causes of zygotic TRD, providing representative examples. The simplest mechanisms of single-locus zygotic TRD are environmental selection (e.g., germination or growth conditions favoring one parental genotype) and inbreeding depression (i.e., selection against one homozygous class independent of background). Both of these mechanisms should cause symmetrical TRD in reciprocal progenies, as they depend solely on an offspring's genotype at the nuclear locus under selection. Hybrid incompatibilities, particularly lethal epistatic interactions within a zygote or between offspring and parent genotypes, are the third common source of zygotic TRD. Asymmetric nuclear–other incompatibilities, in which zygote genotypes interact with the maternal (or otherwise asymmetric) genetic background, can cause strong and apparently single-locus TRD at autosomal nuclear loci. Nuclear–nuclear hybrid incompatibilities (e.g., a recessive lethal interaction that kills one-sixteenth of F_2 progeny) also cause TRD at each locus, though the degree of distortion should be weak if both interacting alleles are recessive. Either kind of incompatibility may also occur in intraspecific (or even intrapopulation, if selfish) contexts, although alleles involved in strong negative epistatic interactions should be rare in well-mixed outbred species.

Environmental selection. Inadvertent selection is likely a common cause of TRD in experimental mapping populations, especially in interpopulation or interspecific crosses. In widespread species of plants (or insects), germination (or eclosion) times may often be locally adapted to distinct temperature or photoperiod cues and thus different among populations, cultivars, or strains. Genotype-specific delay of germination or eclosion under a given growth condition can mimic early mortality as a cause of TRD, especially if only a subset of individuals are genotyped. This possibility was nicely highlighted (and neatly avoided) in a recent study of *Arabidopsis lyrata* that mapped both germination time QTLs and TRDLs in reciprocal backcrosses (56). Because TRDLs and germination time QTLs did not generally overlap, and the former were often dependent on cytoplasmic background (see next section), the authors could infer that intrinsic hybrid seed inviability was the primary source of TRD. However, because alternative genotypes at individual QTLs germinated >10 days apart, this variation could have generated substantial TRD in a study not explicitly monitoring phenology (i.e., if individuals had been included in the mapping set only if they had germinated by a threshold date). A key gene controlling dormancy and germination time in *A. thaliana* (*DOG1*) exhibits TRD in several interpopulation hybrid data sets (132). In addition to phenology, selection for pathogen resistance may also readily contribute to TRD. For example, both of the major TRDLs in a hybrid *Populus* pedigree contained loci encoding resistance to a rust that attacked the hybrid trees (150).

TRD due to inadvertent selection is likely to be exacerbated whenever there are multiple generations of culture prior to genotyping. In a dramatic example, an initially rare (<15%) inversion rose to ~65% in all three treatments (high, low, and control) over six generations of an outbred flower size selection experiment in *M. guttatus*, despite no opportunity for unintended selection on pollen number, seed number, or postgermination survival (74, 87). This remarkable increase could be due to strong gametic selection in heterozygotes (i.e., pollen-killing or pollen competition), but field data suggest that it may in part reflect nonrandom germination under greenhouse conditions (87). In mapping populations, extrinsic selection can be minimized by collecting DNA for genotyping as early in development as possible and avoiding opportunities for bias (e.g., planting just one seed per pot to avoid selecting earlier germinants). On the positive side, researchers can take advantage of TRD to investigate the genetic basis of known differences in germination/eclosion cues between parents (e.g., by genotyping, in bulk or individually, hybrids germinating under different environmental conditions).

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

Inbreeding depression. Inbreeding depression may cause single-locus TRD in any mapping population where homozygosity of lethal or highly deleterious recessive alleles is possible. Thus, inbreeding depression should be rare in line crosses between highly inbred parents (in which strongly deleterious alleles should have been purged during line formation) or in fully outbred mapping populations (in which the risk of parents sharing deleterious mutations is low). Conversely, opportunities for inbreeding depression occur whenever loci heterozygous in the parents become homozygous, such as during RIL formation (and F_2/backcross hybridization if grandparents are shared) from outbred starting materials (25) or in doubled haploid production in plants (47) or animals (80). Even in line crosses with highly inbred parents, however, retention of heterozygosity (which may be particularly likely at loci underlying inbreeding depression) in one parent may allow deleterious recessive alleles to pass harmlessly into an F_1 but segregate in advanced generation hybrids, causing TRD. For example, a retained recessive lethal allele caused substantial single-locus TRD in an early mapping population of *Populus* (12).

Inbreeding depression may be a particularly important source of TRD in outbred taxa with high genetic load and large numbers of progeny per reproductive bout, such as marine invertebrates and coniferous trees (122). TRD in intrapopulation crosses may even be used to measure inbreeding depression; for example, shifts in the degree of distortion among developmental stages cleanly characterized the genetic basis of inbreeding depression in Pacific oysters (123). Similarly, in species with polyembryony and high genetic load (such as conifers), selection against homozygous offspring can cause TRD in even highly outbred populations. A classic example is loblolly pine (*Pinus taeda*), in which selective abortion of inbred embryos within developing seeds significantly skewed genotypic ratios at 19 loci, corresponding to 13 lethal equivalents (128). In these intrapopulation contexts, TRD is a useful tool for the measurement of early-acting inbreeding depression. However, in interpopulation and interspecific crosses, TRD due to inbreeding depression may lead to the incorrect inference of meiotic drive or (more likely) hybrid incompatibility. As next-generation genotyping approaches with power to track all four grandparental alleles make fully outbred mapping populations more common, the latter issue will likely decrease.

Hybrid incompatibilities. Dobzhansky–Muller incompatibilities (DMIs) causing low fitness of particular hybrid genotypic combinations are widespread in crosses among species (and even isolated populations). DMIs fall into two broad categories, nuclear–other (asymmetric) and nuclear–nuclear, that produce distinct patterns of TRD. Epistatic breakdown (and associated TRD) in hybrids can arise through independent evolutionary steps in each lineage (the typical depiction of the Dobzhansky–Muller model) or via two (or more) steps within a single lineage (44, 71, 97, 124). However, even within-lineage coevolution leading to hybrid incompatibility and TRD need not involve TRD (drive) within that species; rather, drift (or adaptive evolution) affecting one component may prompt compensatory evolution by the other (134). Population genetics evidence recently confirmed the theoretical prediction that cytoplasmic male sterility in flowering plant hybrids can arise from selfish mitochondrial evolution and drive nuclear coevolution within one species (22), but it remains an open question how often intraspecific selfish evolution underlies other forms of hybrid incompatibility (and associated TRD).

Nuclear–other DMIs occur when an offspring's diploid nuclear genotype interacts negatively with its F_1 maternal background (e.g., *aa/M_*, where dominant maternal factor *M* and recessive offspring factor *a* are incompatible) or with other factors with asymmetric inheritance or gene expression (e.g., organelles, sex chromosomes, and endosperm or placental tissues). Asymmetry of hybrid incompatibility is a common feature (or even a rule) in the study of species barriers

(144) and can cause strong single-locus distortion at autosomal nuclear loci despite its genetic basis in epistasis. Cytonuclear incompatibilities that reduce offspring survival are particularly widespread (reviewed in 21), and TRD has proven useful in mapping their underlying genetic basis in diverse systems (56, 116). Similarly, parent-of-origin patterns of expression in placental or endosperm tissues (reviewed in 86) may interact negatively with alternative genotypes at nuclear loci in offspring, resulting in differential lethality and zygotic TRD (18, 50, 85). In such cases, distortion and reduced fitness should co-occur in some but not all cross-types. Such asymmetric incompatibilities parallel (in terms of TRD pattern but not necessarily evolutionary process) intraspecific zygotic drive systems. In the best known of these, *Medea* alleles in *Tribolium* flour beetles produce a toxin that kills any offspring not carrying the cotransmitted antidote, resulting in drive of the *Medea* allele (i.e., TRD) in crosses between heterozygous females and noncarrier males (7). Similarly, male-killing by (maternally inherited) *Wolbachia* and *Spiroplasma* bacterial endosymbionts causes biased transmission of sex chromosomes (sex-ratio distortion) in several insects when uninfected males mate with infected females (reviewed in 106). Reciprocal backcrosses are particularly useful for distinguishing such asymmetric postzygotic TRD from strictly gametic mechanisms, as are direct measures of gametic and offspring viability across development. However, distinguishing selfish (and potentially suppressed) zygotic drive systems revealed in interspecific crosses from epistatic hybrid incompatibilities of nonselfish origin is not trivial.

Multilocus nuclear interactions affecting hybrid viability can also cause TRD at one or both epistatic loci, but TRD is predicted to be mild (per generation) if the interacting loci are recessive. For example, complete loss of one double homozygote class (e.g., *aabb* synthetic lethal) in an F_2 population skews allelic transmission only to 56:44 at each locus, a level of distortion that would not be significant (at $\alpha = 0.05$) with fewer than 500 F_2 genotypes. Although such interacting lethals are difficult to detect in F_2 populations via single-locus scans for TRD, they can leave a strong two-locus signal of linkage disequilibrium, especially in advanced generation hybrids (e.g., RILs) or doubled haploid populations (28). For example, reciprocal loss of unlinked gene duplicates causes embryo abortion of the A_{null}/B_{null} double homozygotes in F_2 hybrids between Columbia and Cape Verde accessions of *A. thaliana*; this interaction is phenotypically apparent as inviable seeds in selfed F_1 siliques but was first discovered via two-locus distortion in RILs (10, 137). Similar two-locus distortion is seen in other intraspecific RILs in *Arabidopsis* (143) and in experimental hybrid swarms in the copepod *Tigriopus* (125), consistent with models predicting the accumulation (by drift) of deleterious nuclear–nuclear DMIs in isolated populations. Such incompatibilities are often equated to the evolution of species barriers (136), but negative epistatic interactions causing lethality also occur within populations as a component of inbreeding depression (147) and recessive–recessive DMIs are not strong barriers to gene flow. The recent development of powerful algorithms for the detection of multilocus TRD in dense maps (8, 28) provides hope for the increased detection and further study of interspecific nuclear–nuclear lethal incompatibilities in both plants and animals.

PATTERNS OF TRANSMISSION RATIO DISTORTION IN MAPPING POPULATIONS

To determine what (if any) features of the study system influence the incidence of TRD in mapping populations, we conducted literature reviews of genetic mapping of TRD over two decades (1996–2015). For each data set, we recorded the percentage of mapped markers reported to show significant TRD (at $\alpha = 0.05$ level); we would have liked to also record maximum TRD per locus

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

and the number of distinct distorted regions (TRDLs) but this information was not consistently reported. We then coded each mapping data set for four categorical variables that might be predicted to affect the occurrence of TRD.

1. Predominant marker type [amplified fragment length polymorphism (AFLP) or other dominant fragment-based marker; simple sequence repeat (SSR); single nucleotide polymorphism (SNP)]. Over the past 20 years, markers for assessing segregation have evolved dramatically. Different markers are likely to have different rates of genotyping error, which may be overlaid on the biological signal of TRDLs.
2. Evolutionary context (intraspecific, interspecific). If species are generally more divergent than populations within a species (and TRD is caused primarily by reproductive incompatibilities), interspecific mapping populations might be expected to exhibit higher levels of TRD than intraspecific ones.
3. Taxon (plant, invertebrate, vertebrate, fungus). Reproductive biology sets the stage for prezygotic mechanisms of TRD, so the particular biology of different taxonomic groups could affect the prevalence or strength of TRD.
4. Cross-type (doubled haploid; F_1 hybrid; backcross hybrid; F_2 hybrid; and RIL, NIL, or other advanced generation lines). Each of these crosses has different opportunities for selection, with advanced generation hybrids such as RILs and NILs experiencing repeated rounds of selection.

Results

We obtained data on the frequency of distorted markers (%TRD) from 326 mapping populations in 279 studies published from 1996 to 2015. Over those two decades, the number of papers meeting our criteria ($r^2 = 0.60$) steadily increased, indicating a growing awareness of TRD as a phenomenon worthy of study. Because not all studies yielded complete information for our categories, sample sizes vary as indicated.

As a first pass, we used *t*-tests to compare the incidence of TRD across categories on each of the four axes separately. Neither predominant marker type (dominant, SSR, SNP) nor the evolutionary context (intraspecific versus interspecific) for the cross had any effect on the incidence of TRD in mapped markers ($P > 0.75, N = 322$). There were also no significant differences in mean TRD among our initial taxonomic categories (plants, vertebrates, invertebrates, fungi), but we had low power given the small sample sizes in several categories ($P = 0.19$, $r^2 = 0.006$). Therefore, we regrouped taxa into plants versus animals (dropping the fungi); in this analysis, plants (mean %TRD = 25.67) had a marginally higher incidence of TRD when compared with all animals (mean %TRD = 20.23; $n = 47$; $r^2 = 0.016$, $P = 0.023$) (**Figure 3**). However, there were no animal RIL populations in our data set and only one doubled haploid population. Indeed, cross-type was the most significant factor in the single-axis analyses ($P = 0.0024$, $r^2 = 0.041$, $N = 303$). Doubled haploid populations exhibited the highest incidence of TRD (mean %TRD = 32.85), backcross and F_1 mapping populations were least distorted (mean %TRD = 21.3 and 22.2, respectively), and F_2 and RIL/NIL populations were intermediate (**Figure 3**).

To disentangle taxon and cross-type, we conducted further analyses [general linear model (GLM), Poisson log link] with cross-type nested inside taxon, excluding the one animal doubled haploid study. In this analysis, cross-type within taxon remains significant ($P = 0.004$), with doubled haploid populations (only in plants) again showing the highest incidence of TRD and backcross and F_1 hybrids showing the lowest TRD in both plants and animals. We then excluded doubled haploid and RIL populations to balance the analysis, and ran a two-way GLM (Poisson log link) with taxon, cross-type (backcross, F_1, and F_2 only; $N = 221$), and their interaction. Taxon

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

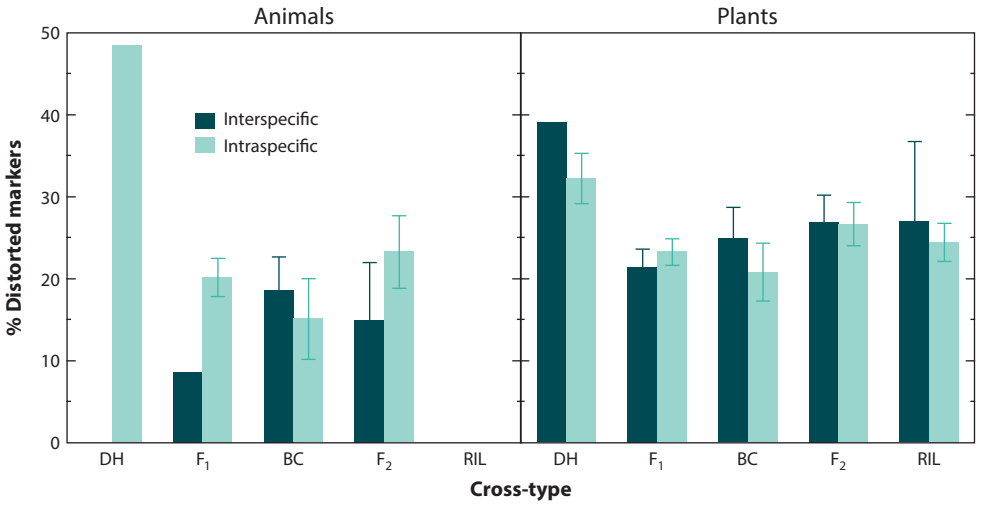

Figure 3

Incidence of TRD (% distorted markers) in a meta-analysis of published mapping populations (1996–2015) categorized by taxon (plant versus animal), cross-type [doubled haploid (DH), F_1 hybrid, F_2 hybrid, backcross hybrid (BC), and advanced generation hybrids (RIL)], and evolutionary context (intraspecific, interspecific). Bars show ±1 SE for each category. Abbreviations: RIL, recombinant inbred line; TRD, transmission ratio distortion.

remains a significant, albeit weak ($P = 0.0495$), predictor of the incidence of TRD, with plants showing greater distortion across all three cross-types (**Figure 3**). Thus, both cross-type and taxon are associated with the incidence of TRD in mapping populations, with doubled haploids particularly prone to TRD and plant maps slightly more distorted, on average, than those in animals.

What Might Account for These Patterns?

The high incidence of TRD in doubled haploid populations points to an important role for inbreeding depression as a major source of locus-specific selection in mapping populations. Inbreeding depression should be particularly acute in doubled haploids, where historically outbred loci become uniformly homozygous in a single generation, and it is thus a plausible explanation for the nearly 50% greater distortion in plant doubled haploid populations versus F_1 and backcross populations. Notably, the one animal doubled haploid population in our data set (30) also exhibited extremely high levels of TRD (48.5% of markers). In contrast, F_2 hybrid and RIL populations (especially in plants) are generally derived from inbred lines that have had the opportunity to purge lethal recessive alleles that can cause TRD. Nonetheless, these results are an important reminder that inbreeding depression, along with more exciting alternatives, must be considered as a candidate source of TRD.

No evidence for elevated amounts of TRD in interspecific versus intraspecific crosses reinforces the conclusion that TRD is not synonymous with the evolution of postmating and postzygotic species barriers. However, no signal from this crude measure of genetic distance on TRD across diverse taxa may also reflect the blurriness of species definitions. Highly cross-compatible taxa may be oversampled in interspecific mapping efforts, while intraspecific crosses (often made for QTL mapping purposes) may be biased toward relatively divergent sets of populations within species. In addition, intraspecific sources of TRD (such as inbreeding depression) may offset increased hybrid incompatibility in interspecific crosses. Our broadscale finding of no

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

effect of genetic distance contrasts with a positive association between the number and magnitude of TRDLs and genetic distance seen across rice subspecies (127). A lack of trend is not surprising, given the many sources of TRD likely operating across diverse systems, but further underlines the complexity of determining the causes of TRD in any single mapping population.

The consistently higher incidence of TRD in plants than in animals, even accounting for cross-type, may have several biological explanations. Plants, in which the haploid male gametophyte (pollen) expresses its own genome (versus that of its diploid parents), may provide additional opportunity for gametic TRD via pollen tube competition and variation in fertilization ability (reviewed in 72). This may be particularly true in crosses between plants with different mating systems and thus different histories of selection on pollen competitive ability and pollen-female interactions (sexual selection) (14). In addition, flowering plants have unique opportunities for postzygotic incompatibilities between embryo and endosperm, as well as nucleocytoplasmic breakdown resulting from selfish organellar evolution (21). Finally, because F_1 male sterility resulting from X-autosomal interactions is common in hybrids between closely related animal species (but uncommon in plants, which mostly lack sex chromosomes) (53), plant mapping populations may generally sample a wider range of parental divergence.

LOOKING FORWARD: NEW APPROACHES TO STUDYING TRANSMISSION RATIO DISTORTION

Although most reports of TRD are by-products of research into other phenomena, non-Mendelian inheritance is worthy of study in its own right. Where possible, controlled crosses that isolate male-specific, female-specific, and genomic background–specific TRD (**Figure 1**) are useful to distinguish meiotic/gametic from zygotic mechanisms and to isolate the effects of sex and cytoplasmic genomes on TRD. Similarly, developmental and fitness data can help distinguish prezygotic (e.g., female meiotic drive or sperm competition) from early zygotic (e.g., differential implantation of embryos or asymmetric postzygotic lethality) mechanisms. However, these traditional genetic approaches can now be complemented by next-generation sequencing approaches that provide new power to rapidly identify distorted genomic regions and characterize stage- and sex-specific mechanisms of distortion using additional mapping populations. For example, a recent study of *Lactuca* (lettuce) followed up the discovery of extreme TRD in reciprocal interspecific backcrossed introgression lines (BILs) with a whole-genome scan of an F_2 population, finding a pattern (as in Reference 76) consistent with a two-locus gametophytic incompatibility killing a subset of both pollen and ovules (51). Such whole-genome comparative TRD mapping promises the rapid discovery of new TRD patterns in diverse taxa, as well as the efficient dissection of the underlying mechanisms.

An exciting extension of the classic bulked segregant analysis, pooled whole-genome sequencing (PoolSeq) of progenies or populations (reviewed in 135), can reveal genome-wide patterns of distortion without individual genotyping (74, 96, 146). PoolSeq creates additional sources of genotyping error (31, 135) and loses individual haplotype information, but it is a powerful approach for estimating differences in allele frequencies in experimentally evolving populations (3, 74) as well as phenotypic cohorts sampled from wild populations (110, 115). PoolSeq of bulked segregants from hybrid mapping populations can provide resolution for QTL mapping (96), but PoolSeq may be uniquely advantageous when TRD per se is the research focus of the mapping effort. Such approaches are particularly useful when an organism or life stage (e.g., insects, seedlings) is numerous but too small for efficient individual genotyping. For example, a recent study of *Drosophila* used large ($N > 1{,}000$) pools of F_1-male and F_1-female backcross progeny to map a putative female meiotic driver causing 54:46 TRD in a centromeric region (146). Such

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

weak distortion would be impossible to detect without the large sample sizes enabled by pooled genotyping but is biologically strong (i.e., the selection coefficient for the overtransmitted allele is >0.15) and could reveal a selfish centromere in action.

Similarly, PoolSeq of gametes (most accessibly sperm) is an exciting new method for diagnosing (or ruling out) stages or mechanisms of TRD. PoolSeq of sperm was first used to test for early-acting sperm-killer loci as a cause of hybrid male sterility in mice (29), although TRD was not detected in either offspring or sperm. More recently, it was used to test among sources of TRD in hybrid mice also segregating for polymorphic hybrid incompatibilities, illustrating the utility of this diagnostic approach (85). In this study, a locus on Chromosome 4 exhibited TRD when F_1 hybrids between two strains of *M. musculus musculus* were backcrossed as males to *M. musculus domesticus*, and was also associated with hybrid male sterility. In such a case, reduced transmission of alleles from the *M. m. musculus* parent (PWK) could be due to an intraspecific sperm killer acting during F_1 spermatogenesis (independent of female genotype), to differential fertilization success of the two alternative sperm haplotypes, or to early death of PWK-carrying progeny during development within the *M. m. domesticus* females. PoolSeq of motile versus immotile F_1 sperm populations cleanly ruled out the first possibility, as there was no evidence of TRD in either sperm pool. This result is particularly important because the Chromosome 4 TRD region shows complex patterns of introgression across both mouse subspecies, and it would be tempting to conclude (without the sperm sequencing data indicating otherwise) that this locus was a gamete killer evolving selfishly in the wild. Creative application of similar PoolSeq approaches to other taxa and tissues holds great promise for dissecting the underlying mechanisms of TRD.

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

SUMMARY POINTS

1. Transmission ratio distortion (TRD) in mapping populations can be a valuable tool for the identification of fascinating genetic phenomena, including inbreeding depression, meiotic drive, gamete competition, and hybrid incompatibility. Therefore, distorted markers should never be removed from genetic maps only because they are distorted.
2. Isolating male-, female-, or zygote-specific distortion with multiple crosses, as well as corroborating hypothesized mechanisms with direct measures of fitness, may be necessary to determine the cause of TRD at a given locus.
3. Across a broad sample, TRD was just as common in within-species as between-species mapping populations, suggesting that it may often reflect inbreeding depression, drive, or population-specific incompatibilities rather than species barriers.
4. Next-generation sequencing techniques make detecting and interpreting TRD in many taxa newly accessible, opening the way to a broader understanding of the prevalence and evolutionary importance of otherwise-hidden processes (such as drive).

FUTURE ISSUES

1. Routine reporting of the number and magnitude of distorted regions in published genetic maps would facilitate broad analyses of the prevalence and patterns of TRD.
2. Pooled whole-genome sequencing of gametes (e.g., sperm, pollen) and offspring (e.g., insect eggs, seedlings) provides powerful new ways to detect, map, and isolate the mechanisms of TRD.

3. Selfish meiotic drive and gamete-killer loci, which have been studied primarily in a few model systems, should now be detectable via mapped TRD in a much broader set of taxa. However, TRD in a mapping population (even if linked to infertility) is not necessarily evidence of a history of selfishness.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We are grateful to F.R. Finseth, E.L. Larson, J.K. Kelly, and A.G. Clark for helpful comments on the manuscript. Funding support from National Science Foundation grants OIA-1736249, DEB-1457763, and DGE-1841053 made preparation of this article possible.

LITERATURE CITED

1. Akera T, Chmátal L, Trimm E, Yang K, Aonbangkhen C, et al. 2017. Spindle asymmetry drives non-Mendelian chromosome segregation. *Science* 358:668–72
2. Akera T, Trimm E, Lampson M. 2018. Molecular and evolutionary strategies of meiotic cheating by selfish centromeres. bioRxiv 405068. **https://doi.org/10.1101/405068**
3. Barrick JE, Yu DS, Yoon SH, Jeong H, Oh TK, et al. 2009. Genome evolution and adaptation in a long-term experiment with *Escherichia coli*. *Nature* 461:1243–47
4. Beavis WD. 1994. The power and deceit of QTL experiments: lessons from comparative QTL studies. In *Proceedings of the 49th Annual Corn and Sorghum Industry Research Conference ASTA*, Washington, DC, pp. 252–68
5. Becker T, Knapp M. 2004. A powerful strategy to account for multiple testing in the context of haplotype analysis. *Am. J. Hum. Genet.* 75:561–70
6. Bedinger PA, Broz AK, Tovar-Mendez A, McClure B. 2017. Pollen-pistil interactions and their role in mate selection. *Plant Physiol.* 173:79–90
7. Beeman RW, Friesen KS, Denell RE. 1992. Maternal-effect selfish genes in flour beetles. *Science* 256:89–92
8. Behrouzi P, Wit EC. 2018. Detecting epistatic selection with partially observed genotype data by using copula graphical models. *J. R. Stat. Soc. C* 68:141–60
9. Bernasconi G, Ashman T-L, Birkhead TR, Bishop JDD, Grossniklaus U, et al. 2004. Evolutionary ecology of the prezygotic stage. *Science* 303:971–75
10. Bikard D, Patel D, Le Metté C, Giorgi V, Camilleri C, et al. 2009. Divergent evolution of duplicate genes leads to genetic incompatibilities within *A. thaliana*. *Science* 323:623–26
11. Birchler JA, Dawe R, Doebley JF. 2003. Marcus Rhoades, preferential segregation and meiotic drive. *Genetics* 164:835–41
12. Bradshaw HD Jr., Stettler RF. 1994. Molecular genetics of growth and development in *Populus*. II. Segregation distortion due to genetic load. *Theor. Appl. Genet.* 89:551–58
13. Brandt DYC, Aguiar VRC, Bitarello BD, Nunes K, Goudet J, Meyer D. 2015. Mapping bias overestimates reference allele frequencies at the *HLA* genes in the 1000 Genomes Project phase I data. *Genes Genom. Genet.* 5:931–41
14. Brandvain Y, Haig D. 2005. Divergent mating systems and parental conflict as a barrier to hybridization in flowering plants. *Am. Nat.* 166:330–38
15. Bravo Núñez MA, Nuckolls NL, Zanders SE. 2018. Genetic villains: killer meiotic drivers. *Trends Genet.* 34:424–33

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

16. Broman KW, Wu H, Sen S, Churchill GA. 2003. R/qtl: QTL mapping in experimental crosses. *Bioinformatics* 19:889–90
17. Buckler ES IV, Phelps-Durr TL, Buckler CSK, Dawe R, Doebley JF, Holtsford TP. 1999. Meiotic drive of chromosomal knobs reshaped the maize genome. *Genetics* 153:415–26
18. Burkart-Waco D, Josefsson C, Dilkes B, Kozloff N, Torjek O, et al. 2012. Hybrid incompatibility in *Arabidopsis* is determined by a multiple-locus genetic network. *Plant Physiol.* 158:801–12
19. Burt A, Trivers R. 1998. Selfish DNA and breeding system in flowering plants. *Proc. R. Soc. B* 265:141–46
20. Burt A, Trivers R. 2006. *Genes in Conflict*. Cambridge, MA: Belknap Press
21. Burton RS, Pereira RJ, Barreto FS. 2013. Cytonuclear genomic interactions and hybrid breakdown. *Annu. Rev. Ecol. Evol. Syst.* 44:281–302
22. Case AL, Finseth FR, Barr CM, Fishman L. 2016. Selfish evolution of cytonuclear hybrid incompatibility in *Mimulus*. *Proc. R. Soc. B* 283:20161493
23. Casellas J, Gularte RJ, Farber CR, Varona L, Mehrabian M, et al. 2012. Genome scans for transmission ratio distortion regions in mice. *Genetics* 191:247–59
24. Casellas J, Manunza A, Mercader A, Quintanilla R, Amills M. 2014. A flexible Bayesian model for testing for transmission ratio distortion. *Genetics* 198:1357–67
25. Chapman MA, Hiscock SJ, Filatov DA. 2016. The genomic bases of morphological divergence and reproductive isolation driven by ecological speciation in *Senecio* (Asteraceae). *J. Evol. Biol.* 29:98–113
26. Chmátal L, Gabriel SI, Mitsainas GP, Martínez-Vargas J, Ventura J, et al. 2014. Centromere strength provides the cell biological basis for meiotic drive and karyotype evolution in mice. *Curr. Biol.* 24:2295–300
27. Christiansen FB, Frydenberg O. 1973. Selection component analysis of natural polymorphisms using population samples including mother-offspring combinations. *Theor. Popul. Biol.* 4:425–45
28. Colomé-Tatché M, Johannes F. 2016. Signatures of Dobzhansky–Muller incompatibilities in the genomes of recombinant inbred lines. *Genetics* 202:825–41
29. Corbett-Detig R, Jacobs-Palmer E, Hartl D, Hoekstra H. 2015. Direct gamete sequencing reveals no evidence for segregation distortion in house mouse hybrids. *PLOS ONE* 10:e0131933-13
30. Cui Y, Wang H, Qiu X, Liu H, Yang R. 2015. Bayesian analysis for genetic architectures of body weights and morphological traits using distorted markers in Japanese flounder *Paralichthys olivaceus*. *Mar. Biotechnol.* 17:693–702
31. Cutler DJ, Jensen JD. 2010. To pool, or not to pool? *Genetics* 186:41–43
32. Dawe R, Hiatt EN. 2004. Plant neocentromeres: fast, focused, and driven. *Chromosome Res.* 12:655–69
33. Dawe R, Lowry EG, Gent JI, Stitzer MC, Swentowsky KW, et al. 2018. A kinesin-14 motor activates neocentromeres to promote meiotic drive in maize. *Cell* 173:839–50
34. de Koning D-J, McIntyre LM. 2017. Back to the future: Multiparent populations provide the key to unlocking the genetic basis of complex traits. *Genes Genom. Genet.* 7:1617–18
35. Diaz A, MacNair MR. 1999. Pollen tube competition as a mechanism of prezygotic reproductive isolation between Mimulus nasutus and its presumed progenitor M. guttatus. *New Phytol.* 144:471–78
36. Didion JP, Morgan AP, Clayshulte AMF, McMullan RC, Yadgary L, et al. 2015. A multi-megabase copy number gain causes maternal transmission ratio distortion on mouse chromosome 2. *PLOS Genet.* 11:e1004850
37. Didion JP, Morgan AP, Yadgary L, Bell TA, McMullan RC, et al. 2016. R2d2 drives selfish sweeps in the house mouse. *Mol. Biol. Evol.* 33:1381–95
38. Eshel I. 1985. Evolutionary genetic stability of Mendelian segregation and the role of free recombination in the chromosomal system. *Am. Nat.* 125:412–20
39. Fishman L, Aagaard JE, Tuthill JC. 2008. Toward the evolutionary genomics of gametophytic divergence: Patterns of transmission ratio distortion in monkeyflower (*Mimulus*) hybrids reveal a complex genetic basis for conspecific pollen precedence. *Evolution* 62:2958–70
40. Fishman L, Kelly AJ, Morgan E, Willis JH. 2001. A genetic map in the *Mimulus guttatus* species complex reveals transmission ratio distortion due to heterospecific interactions. *Genetics* 159:1701–16
41. Fishman L, Kelly JK. 2015. Centromere-associated meiotic drive and female fitness variation in *Mimulus*. *Evolution* 69:1208–18

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

42. Fishman L, Saunders A. 2008. Centromere-associated female meiotic drive entails male fitness costs in monkeyflowers. 322:1559–62
43. Fishman L, Stathos A, Beardsley P, Williams CF, Hill JP. 2013. Chromosomal rearrangements and the genetics of reproductive barriers in *Mimulus* (monkeyflowers). *Evolution* 67:2547–60
44. Fishman L, Sweigart AL. 2018. When two rights make a wrong: the evolutionary genetics of plant hybrid incompatibilities. *Annu. Rev. Plant Biol.* 69:701–37
45. Fishman L, Willis JH. 2005. A novel meiotic drive locus almost completely distorts segregation in *Mimulus* (monkeyflower) hybrids. *Genetics* 169:347–53
46. Flanagan SP, Jones AG. 2017. Genome-wide selection components analysis in a fish with male pregnancy. *Evolution* 71:1096–105
47. Forster BP, Heberle-Bors E, Kasha KJ, Touraev A. 2007. The resurgence of haploids in higher plants. *Trends Plant Sci.* 12:368–75
48. Frank SA. 1991. Divergence of meiotic drive-suppression systems as an explanation for sex-biased hybrid sterility and inviability. *Evolution* 45:262–67
49. Gagnaire P-A, Normandeau E, Pavey SA, Bernatchez L. 2013. Mapping phenotypic, expression and transmission ratio distortion QTL using RAD markers in the lake whitefish (*Coregonus clupeaformis*). *Mol. Ecol.* 22:3036–48
50. Garner AG, Kenney AM, Fishman L, Sweigart AL. 2016. Genetic loci with parent-of-origin effects cause hybrid seed lethality in crosses between *Mimulus* species. *New Phytol.* 211:319–31
51. Giesbers AKJ, den Boer E, Ulen JJWEH, van Kaauwen MPW, Visser RGF, et al. 2019. Patterns of transmission ratio distortion in interspecific lettuce hybrids reveal a sex-independent gametophytic barrier. *Genetics* 211:263–76
52. Gowaty PA, Anderson WW, Bluhm CK, Drickamer LC, Kim Y-K, Moore AJ. 2007. The hypothesis of reproductive compensation and its assumptions about mate preferences and offspring viability. *PNAS* 104:15023–27
53. Haldane JBS. 1922. Sex ratio and unisexual sterility in hybrid animals. *J. Genet.* 12:101–9
54. Haldane JBS. 1932. *The Causes of Evolution*. London: Longmans, Green and Co.
55. Hall DW, Dawe R. 2018. Modeling the evolution of female meiotic drive in maize. *Genes Genom. Genet.* 8:123–30
56. Hämälä T, Mattila TM, Leinonen PH, Kuittinen H, Savolainen O. 2017. Role of seed germination in adaptation and reproductive isolation in *Arabidopsis lyrata*. *Mol. Ecol.* 26:3484–96
57. Hamlin JAP, Sherman NA, Moyle LC. 2017. Two loci contribute epistastically to heterospecific pollen rejection, a postmating isolating barrier between species. *Genes Genom. Genet.* 7:2151–59
58. Hammond TM, Rehard DG, Xiao H, Shiu PKT. 2012. Molecular dissection of *Neurospora* spore killer meiotic drive elements. *PNAS* 109:12093–98
59. Helleu Q, Gérard PR, Montchamp-Moreau C. 2014. Sex chromosome drive. *Cold Spring Harb. Perspect. Biol.* 7:a017616
60. Henikoff S, Malik H. 2002. Selfish drivers. *Nature* 417:227
61. Hiatt EN, Dawe R. 2003. Four loci on abnormal chromosome 10 contribute to meiotic drive in maize. *Genetics* 164:699–709
62. Higashiyama T, Takeuchi H. 2015. The mechanism and key molecules involved in pollen tube guidance. *Annu. Rev. Plant Biol.* 66:393–413
63. Higgins DM, Lowry EG, Kanizay LB, Becraft PW, Hall DW, Dawe R. 2018. Fitness costs and variation in transmission distortion associated with the abnormal chromosome 10 meiotic drive system in maize. *Genetics* 208:297–305
64. Hu W, Jiang Z-D, Suo F, Zheng J-X, He W-Z, Du L-L. 2017. A large gene family in fission yeast encodes spore killers that subvert Mendel's law. *eLife* 6:e26057
65. Huang LO, Labbe A, Infante-Rivard C. 2013. Transmission ratio distortion: review of concept and implications for genetic association studies. *Hum. Genet.* 132:245–63
66. Hurst GD, Werren JH. 2001. The role of selfish genetic elements in eukaryotic evolution. *Nat. Rev. Genet.* 2:597–606

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

67. Hurst LD, Pomiankowski A. 1991. Causes of sex ratio bias may account for unisexual sterility in hybrids: a new explanation for Haldane's rule and related phenomena. *Genetics* 128:841–58
68. Immler S, Otto SP. 2018. The evolutionary consequences of selection at the haploid gametic stage. *Am. Nat.* 192:241–49
69. Iwata-Otsubo A, Dawicki-McKenna JM, Akera T, Falk SJ, Chmátal L, et al. 2017. Expanded satellite repeats amplify a discrete CENP-A nucleosome assembly site on chromosomes that drive in female meiosis. *Curr. Biol.* 27:2365–68
70. Jaenike J. 2001. Sex chromosome meiotic drive. *Annu. Rev. Genet.* 32:25–49
71. Johnson NA. 2010. Hybrid incompatibility genes: remnants of a genomic battlefield? *Trends Genet.* 26:317–25
72. Joseph SB, Kirkpatrick M. 2004. Haploid selection in animals. *Trends Ecol. Evol.* 19:592–97
73. Kanizay LB, Pyhäjärvi T, Lowry EG, Hufford MB, Peterson DG, et al. 2013. Diversity and abundance of the abnormal chromosome 10 meiotic drive complex in *Zea mays*. *Heredity* 110:570–77
74. Kelly JK, Koseva B, Mojica JP. 2013. The genomic signal of partial sweeps in *Mimulus guttatus*. *Genome Biol. Evol.* 5:1457–69
75. Kermicle JL. 2006. A selfish gene governing pollen-pistil compatibility confers reproductive isolation between maize relatives. *Genetics* 172:499–506
76. Kerwin RE, Sweigart AL. 2017. Mechanisms of transmission ratio distortion at hybrid sterility loci within and between *Mimulus* species. *Genes Genom. Genet.* 7:3719–30
77. Knief U, Schielzeth H, Ellegren H, Kempenaers B, Forstmeier W. 2015. A prezygotic transmission distorter acting equally in female and male zebra finches *Taeniopygia guttata*. *Mol. Ecol.* 24:3846–59
78. Koide Y, Onishi K, Nishimoto D, Baruah AR, Kanazawa A, Sano Y. 2008. Sex-independent transmission ratio distortion system responsible for reproductive barriers between Asian and African rice species. *New Phytol.* 179:888–900
79. Koide Y, Shinya Y, Ikenaga M, Sawamura N, Matsubara K, et al. 2012. Complex genetic nature of sex-independent transmission ratio distortion in Asian rice species: the involvement of unlinked modifiers and sex-specific mechanisms. *Heredity* 108:242–47
80. Komen H, Thorgaard GH. 2007. Androgenesis, gynogenesis and the production of clones in fishes: a review. *Aquaculture* 269:150–73
81. Kosman ET, Levitan DR. 2014. Sperm competition and the evolution of gametic compatibility in externally fertilizing taxa. *Mol. Hum. Reprod.* 20:1190–97
82. Kursel LE, Malik H. 2018. The cellular mechanisms and consequences of centromere drive. *Curr. Opin. Cell Biol.* 52:58–65
83. Lampson MA, Black BE. 2017. Cellular and molecular mechanisms of centromere drive. *Cold Spring Harb. Symp. Quant. Biol.* 82:249–57
84. Larracuente AM, Presgraves DC. 2012. The selfish *Segregation Distorter* gene complex of *Drosophila melanogaster*. *Genetics* 192:33–53
85. Larson EL, Vanderpool D, Sarver BAJ, Callahan C, Keeble S, et al. 2018. The evolution of polymorphic hybrid incompatibilities in house mice. *Genetics* 209:845–59
86. Lawson HA, Cheverud JM, Wolf JB. 2013. Genomic imprinting and parent-of-origin effects on complex traits. *Nat. Rev. Genet.* 14:609–17
87. Lee YW, Fishman L, Kelly JK, Willis JH. 2016. A segregating inversion generates fitness variation in yellow monkeyflower (*Mimulus guttatus*). *Genetics* 202:1473–84
88. Leigh EG. 1977. How does selection reconcile individual advantage with the good of the group? *PNAS* 74:4542–46
89. Levitan DR. 2018. Do sperm really compete and do eggs ever have a choice? Adult distribution and gamete mixing influence sexual selection, sexual conflict, and the evolution of gamete recognition proteins in the sea. *Am. Nat.* 191:88–105
90. Li G, Serba DD, Saha MC, Bouton JH, Lanzatella CL, Tobias CM. 2014. Genetic linkage mapping and transmission ratio distortion in a three-generation four-founder population of *Panicum virgatum* (L.). *Genes Genom. Genet.* 4:913–23

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

91. Lindholm AK, Dyer KA, Firman RC, Fishman L, Forstmeier W, et al. 2016. The ecology and evolutionary dynamics of meiotic drive. *Trends Ecol. Evol.* 31:315–26
92. Liu Y, Zhang L, Xu S, Hu L, Hurst LD, Kong X. 2013. Identification of two maternal transmission ratio distortion loci in pedigrees of the Framingham Heart Study. *Sci. Rep.* 3:2147
93. Lorieux M, Goffinet B, Perrier X, González de León D, Lanaud C. 1995. Maximum-likelihood models for mapping genetic markers showing segregation distortion. 1. Backcross populations. *Theor. Appl. Genet.* 90:73–80
94. Lyon MF. 2003. Transmission ratio distortion in mice. *Annu. Rev. Genet.* 37:393–408
95. Lyttle TW. 1991. Segregation distorters. *Annu. Rev. Genet.* 25:511–57
96. Magwene PM, Willis JH, Kelly JK. 2011. The statistics of bulk segregant analysis using next generation sequencing. *PLOS Comput. Biol.* 7:e1002255
97. Maheshwari S, Barbash DA. 2011. The genetics of hybrid incompatibilities. *Annu. Rev. Genet.* 45:331–55
98. Malik H. 2005. *Mimulus* finds centromeres in the driver's seat. *Trends Ecol. Evol.* 20:151–54
99. Malik H, Henikoff S. 2001. Adaptive evolution of Cid, a centromere-specific histone in Drosophila. *Genetics* 157:1293–98
100. Malik H, Henikoff S. 2002. Conflict begets complexity: the evolution of centromeres. *Curr. Opin. Genet. Dev.* 12:711–18
101. Manser A, König B, Lindholm AK. 2015. Female house mice avoid fertilization by *t* haplotype incompatible males in a mate choice experiment. *J. Evol. Biol.* 28:54–64
102. Manser A, Lindholm AK, König B, Bagheri HC. 2011. Polyandry and the decrease of a selfish genetic element in a wild house mouse population. *Evolution* 65:2435–47
103. Manser A, Lindholm AK, Simmons LW, Firman RC. 2017. Sperm competition suppresses gene drive among experimentally evolving populations of house mice. *Mol. Ecol.* 26:5784–92
104. Mazer SJ, Hove AA, Miller BS, Barbet-Massin M. 2010. The joint evolution of mating system and pollen performance predictions regarding male gametophytic evolution in selfers versus outcrossers. *Perspect. Plant Ecol. Evol. Syst.* 12:31–41
105. McDaniel SF, Willis JH, Shaw AJ. 2007. A linkage map reveals a complex basis for segregation distortion in an interpopulation cross in the moss *Ceratodon purpureus*. *Genetics* 176:2489–500
106. McLaughlin RN, Malik H. 2017. Genetic conflicts: the usual suspects and beyond. *J. Exp. Biol.* 220(Part 1):6–17
107. Meiklejohn CD, Tao Y. 2010. Genetic conflict and sex chromosome evolution. *Trends Ecol. Evol.* 25:215–23
108. Møller AP. 1998. *Sperm Competition and Sexual Selection*. San Diego, CA: Academic. 1st ed.
109. Monnahan PJ, Colicchio J, Kelly JK. 2015. A genomic selection component analysis characterizes migration-selection balance within a hybrid *Mimulus* population. *Evolution* 69:1713–27
110. Monnahan PJ, Kelly JK. 2017. The genomic architecture of flowering time varies across space and time in *Mimulus guttatus*. *Genetics* 206:1621–35
111. Moore JC, Pannell JR. 2011. Sexual selection in plants. *Curr. Biol.* 21:R176–82
112. Moyle LC. 2006. Genome-wide associations between hybrid sterility QTL and marker transmission ratio distortion. *Mol. Biol. Evol.* 23:973–80
113. Moyle LC, Jewell CP, Kostyun JL. 2014. Fertile approaches to dissecting mechanisms of premating and postmating prezygotic reproductive isolation. *Curr. Opin. Plant Biol.* 18:16–23
114. Nadeau JH. 2017. Do gametes woo? Evidence for their nonrandom union at fertilization. *Genetics* 207:369–87
115. Nelson TC, Monnahan PJ, McIntosh MK, Anderson K, MacArthur-Waltz E, et al. 2019. Extreme copy number variation at a tRNA ligase gene affecting phenology and fitness in yellow monkeyflowers. *Mol. Ecol.* 28:1460–75
116. Niehuis O, Judson AK, Gadau J. 2008. Cytonuclear genic incompatibilities cause increased mortality in male F_2 hybrids of *Nasonia giraulti* and *N. vitripennis*. *Genetics* 178:413–26
117. Nuckolls NL, Bravo Núñez MA, Eickbush MT, Young JM, Lange JJ, et al. 2017. *wtf* genes are prolific dual poison-antidote meiotic drivers. *eLife* 6:2235

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

118. Pannell JR, Labouche A-M. 2013. The incidence and selection of multiple mating in plants. *Philos. Trans. R. Soc. B* 368:20120051
119. Pardo-Manuel de Villena F, Sapienza C. 2001. Female meiosis drives karyotypic evolution in mammals. *Genetics* 159:1179–89
120. Pardo-Manuel de Villena F, Sapienza C. 2001. Nonrandom segregation during meiosis: the unfairness of females. *Mamm. Genome* 12:331–39
121. Pease JB, Guerrero RF, Sherman NA, Hahn MW, Moyle LC. 2016. Molecular mechanisms of postmating prezygotic reproductive isolation uncovered by transcriptome analysis. *Mol. Ecol.* 25:2592–608
122. Plough LV. 2016. Genetic load in marine animals: a review. *Curr. Zool.* 62:567–79
123. Plough LV, Hedgecock D. 2011. Quantitative trait locus analysis of stage-specific inbreeding depression in the Pacific oyster *Crassostrea gigas*. *Genetics* 189:1473–86
124. Presgraves DC. 2010. The molecular evolutionary basis of species formation. *Nat. Rev. Genet.* 11:175–80
125. Pritchard VL, Dimond L, Harrison JS, Velázquez CCS, Zieba JT, et al. 2011. Interpopulation hybridization results in widespread viability selection across the genome in *Tigriopus californicus*. *BMC Genet.* 12:54
126. Puzey JR, Willis JH, Kelly JK. 2017. Population structure and local selection yield high genomic variation in *Mimulus guttatus*. *Mol. Ecol.* 26:519–35
127. Reflinur, Kim B, Jang SM, Chu S-H, Bordiya Y, et al. 2014. Analysis of segregation distortion and its relationship to hybrid barriers in rice. *Rice* 7:3
128. Remington DL, O'Malley DM. 2000. Whole-genome characterization of embryonic stage inbreeding depression in a selfed loblolly pine family. *Genetics* 155:337–48
129. Rick CM. 1966. Abortion of male and female gametes in the tomato determined by allelic interaction. *Genetics* 53:85–96
130. Robertson AW, Mountjoy C, Faulkner BE, Roberts MV, Macnair MR. 1999. Bumble bee selection of *Mimulus guttatus* flowers: the effects of pollen quality and reward depletion. *Ecology* 80:2594–606
131. Rosin LF, Mellone BG. 2017. Centromeres drive a hard bargain. *Trends Genet.* 33:101–17
132. Salome PA, Bomblies K, Laitinen RAE, Yant L, Mott R, Weigel D. 2011. Genetic architecture of flowering-time variation in *Arabidopsis thaliana*. *Genetics* 188:421–33
133. Sarver BAJ, Keeble S, Cosart T, Tucker PK, Dean MD, Good JM. 2017. Phylogenomic insights into mouse evolution using a pseudoreference approach. *Genome Biol. Evol.* 9:726–39
134. Satyaki PRV, Cuykendall TN, Wei KHC, Brideau NJ, Kwak H, et al. 2014. The *Hmr* and *Lhr* hybrid incompatibility genes suppress a broad range of heterochromatic repeats. *PLOS Genet.* 10:e1004240-22
135. Schlötterer C, Tobler R, Kofler R, Nolte V. 2014. Sequencing pools of individuals—mining genome-wide polymorphism data without big funding. *Nat. Rev. Genet.* 15:749–63
136. Simon M, Durand S, Pluta N, Gobron N, Botran L, et al. 2016. Genomic conflicts that cause pollen mortality and raise reproductive barriers in *Arabidopsis thaliana*. *Genetics* 203:1353–67
137. Simon M, Loudet O, Durand S, Bérard A, Brunel D, et al. 2008. Quantitative trait loci mapping in five new large recombinant inbred line populations of *Arabidopsis thaliana* genotyped with consensus single-nucleotide polymorphism markers. *Genetics* 178:2253–64
138. Swanson R, Edlund AF, Preuss D. 2004. Species specificity in pollen-pistil interactions. *Annu. Rev. Genet.* 38:793–818
139. Sweigart AL, Brandvain Y, Fishman L. 2019. Making a murderer: on the evolutionary framing of hybrid gamete-killers. *Trends Genet.* 35:245–52
140. Sweigart AL, Fishman L, Willis JH. 2006. A simple genetic incompatibility causes hybrid male sterility in *Mimulus*. *Genetics* 172:2465–79
141. Taylor DR, Ingvarsson PK. 2003. Common features of segregation distortion in plants and animals. *Genetica* 117:27–35
142. Thépot S, Restoux G, Goldringer I, Hospital F, Gouache D, et al. 2015. Efficiently tracking selection in a multiparental population: the case of earliness in wheat. *Genetics* 199:609–23
143. Törjék O, Witucka-Wall H, Meyer RC, von Korff M, Kusterer B, et al. 2006. Segregation distortion in *Arabidopsis* C24/Col-o and Col-o/C24 recombinant inbred line populations is due to reduced fertility caused by epistatic interaction of two loci. *Theor. Appl. Genet.* 113:1551–61

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

144. Turelli M, Moyle LC. 2007. Asymmetric postmating isolation: Darwin's corollary to Haldane's rule. *Genetics* 176:1059–88
145. Van Ooijen J. 2006. *JoinMap 4.0: software for the calculation of genetic linkage maps in experimental populations*. Wageningen, Neth.: Kyazma B.V. **https://www.kyazma.nl/index.php/JoinMap/**
146. Wei KHC, Reddy HM, Rathnam C, Lee J, Lin D, et al. 2017. A pooled sequencing approach identifies a candidate meiotic driver in *Drosophila*. *Genetics* 206:451–65
147. Willis JH. 1992. Genetic analysis of inbreeding depression caused by chlorophyll-deficient lethals in *Mimulus guttatus*. *Heredity* 69:562–72
148. Xu S. 2003. Theoretical basis of the Beavis effect. *Genetics* 165:2259–68
149. Xu S. 2008. Quantitative trait locus mapping can benefit from segregation distortion. *Genetics* 180:2201–8
150. Yin TM, DiFazio SP, Gunter LE, Riemenschneider D, Tuskan GA. 2004. Large-scale heterospecific segregation distortion in *Populus* revealed by a dense genetic map. *Theor. Appl. Genet.* 109:451–63

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

Annual Review of Genetics

Volume 53, 2019

Contents

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.

Errata

An online log of corrections to Annual Review of Genetics articles may be found at http://www.annualreviews.org/errata/genet

Annu. Rev. Genet. 2019.53:347-372. Downloaded from www.annualreviews.org
Access provided by University of Montana on 09/28/20. For personal use only.