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ARTICLE

The evolutionary significance of meiotic drive

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Of the laws of inheritance attributed to Gregor Mendel the first is the Law of Segregation: that the two alleles in a heterozygote have an equal chance of contributing to its gametes. In this essay, we will consider circumstances, documented in animals and plants, where there is bias in favour of one type of allele over another in transmission, thereby breaking the first law. That violation of his law is no bad reflection on Mendel's astonishing insight; indeed his law forms the valued null hypothesis that leads to further understanding of the complexity of inheritance. The deviation from 1:1 transmission is commonly termed 'meiotic drive' whether the anomaly arises from a meiotic process or at a post-meiotic stage of gametogenesis (Zimmering et al. 1970). Indeed some of the best studied meiotic drive systems—particularly in animals (e.g. *Segregation Distorter* in *Drosophila melanogaster* and *t*-haplotypes in *Mus musculus*)—involve interactions among the four products of meiosis in males with chemical destruction of the two spermatids carrying one allele by the two spermatids carrying the other; hence the term 'killer meiotic drive' (Zanders and Unckless 2019). In this essay, we will focus on 'true meiotic drive' where the distorted transmission does arise within meiosis itself (Zanders and Unckless 2019), specifically in females. Here, the non-transmission of one of the products of meiotic division is inherent in the gametogenic process—with the formation of a polar body as the functionless by-product of division, with the egg continuing on as the viable entity. The meiotic drive is therefore the biased segregation in favour of one type of allele such that it is most commonly retained in the egg at the cost of the other type of allele, which most commonly ends up in the polar body. The biased segregation can occur at either the first or second division of meiosis—both of which generate a functionless polar body, such that there is ultimately only one viable product of the two divisions—the final version of the egg, which then becomes a zygote on fertilisation. Alleles that show meiotic drive are often termed 'cheaters' (Lyttle 1993) or 'selfish' genetic elements (Lindholm et al. 2016; Fishman and McIntosh 2019). Because of the winner-loser aspect of female meiosis (the losing allele going into the polar body, the winner staying in the egg), the system appears readily exploitable by those cheating alleles—all else being equal, selection would seem to strongly favour cheating (where 'cheating' is defying the equal transmission of alleles from heterozygotes expected under Mendel's first law). On these grounds, it is probable that true meiotic drive in females has occurred frequently over evolutionary time, and that this frequency of occurrence has perhaps been hugely underestimated.

How might a cheater allele be able to bias its transmission into the gamete at the cost of another allele in true meiotic drive? The most obvious locus to have a cheater allele would be one that can modulate the transmission of the whole chromosomes on which it resides, whether it be the homologous chromosomes that segregate at meiosis I or the chromatids that segregate at meiosis II. An ability to bias segregation of whole chromosomes is the basis of the 'centromere drive' hypothesis. This hypothesis is posited as a chromosome with a larger centromere being better able to orientate favourably on the meiotic spindle than a chromosome with a smaller centromere, such that it is more frequently retained in the egg rather than the polar body (Henikoff et al. 2001). The centromere consists of the DNA of the chromosome (the centromeric region) and a mass of centromeric proteins that interact with the microtubules of the spindle. Thus, the centromeric region could be the locus with the cheater allele (organising a large centromere) that transmits better than the alternative allele (organising a small centromere). As well as having a large or small centromere being the alternative alleles associated with the tendency for a chromosome to segregate to the oocyte or polar body respectively, the alternative alleles could be presence or absence of an extra chromosomal region that can interact with spindle microtubules (a neocentromere)(Dawe and Hiatt 2004). Again having that neocentromere could provide an advantage in segregation of the chromosome on the meiotic spindle. In a situation of heterozygosity for a large and small centromere, the two chromatids in each homologue at meiosis I will have the same sized centromere (one homologue with two chromatids both with large centromeres and the other homologue likewise with small centromeres). This means that the meiotic drive will be at meiosis I in this type of heterozygosity. In the case of heterozygosity for presence/absence of a neocentromere, the DNA location for the neocentromere may be well-separated from the true centromere, such that recombination could lead to both homologues having a neocentromere on one of their two chromatids (Fishman and McIntosh 2019; Lamelza and Lampson 2020). This could lead to meiotic drive at meiosis II—instead of the two homologues at metaphase I having a difference of presence/absence of the neocentromere, it is the two chromatids at metaphase II that differ in this way.

One can imagine that having a different sized centromere could create a differing tendency to segregate on the egg side of the meiotic spindle vs. the cortical side (where the polar body forms), and likewise in having presence/absence of a neocentromere, but how, mechanistically does this happen? Here we need to turn to some of the latest empirical studies. Recent work in the house

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mouse have confirmed that when there is heterozygosity for centromere size, the larger centromere (as determined by quantity of centromeric proteins) has a greater tendency to segregate to the egg, and the smaller centromere to the polar body, at meiosis I (Chmátal et al. 2014). Further, there is biochemical asymmetry in the spindle between the egg side of the spindle and the cortical side in the mouse (Akera et al. 2017) and larger centromeres show greater instability in microtubule attachment which creates a tendency for them to relocate on the egg side of the spindle, should they be positioned otherwise (Akera et al. 2019). Likewise, recent work in maize *Zea mays* has produced a mechanistic basis for the biased segregation of a neocentromere to the egg over the polar body, at meiosis II. In this case, the neocentromere does not form a proteinaceous kinetochore for binding with the microtubules, but it organises molecular motors which preferentially walk it along microtubules to the egg spindle pole (Swentowsky et al. 2020; Lamelza and Lampson 2020). The neocentromere orientates to the egg pole very quickly and it appears that the resulting tension rotates the normal centromere to the same pole (Dawe and Hiatt 2004; Swentowsky et al. 2020). This provides an explanation why the chromosome bridge and breakage sequence that can occur in dicentrics does not happen under these circumstances in maize; nor are there issues at mitosis, because the neocentromeres are meiosis-specific (Dawe and Hiatt 2004).

Through being favoured by true meiotic drive, there is a likelihood that a newly arisen cheater allele will sweep through the population to fixation. Whether and how fast this happens depends on a number of factors: the extent of the bias away from 1:1 transmission, population size, if there is any fertility disadvantage associated with the cheater allele and the extent of that disadvantage, and if there is counteracting drive suppression. Some of these factors will be expanded upon below. True meiotic drive as a process fixing new variants has particularly been promulgated with respect to chromosomal rearrangements; indeed MJD White (1968) made it a key part of his stasipatric speciation model, which emphasised the primary role of novel chromosomal rearrangements in speciation. Chromosomal rearrangements and their ancestral homologues may suffer heterozygote disadvantage (underdominance) through pairing and segregation anomalies at meiosis I (Searle 1993), which would disfavour the new rearrangement until it crosses the 50% threshold in a population. White saw true meiotic drive as the way that rearrangements could cross that threshold. Theoretical mathematical analyses by Hedrick (1981) and Walsh (1982) confirmed that that indeed could occur. The hurdle is not always high, as some rearrangements show little underdominance (Searle 1993).

Cheater alleles do not necessarily go to fixation through true meiotic drive. A recent interesting empirical example is the *R2d2* locus in the house mouse (Didion et al. 2015, 2016). The properties of this locus were discovered in a set of mice generated by a highly organised regime of intercrossing of eight founder inbred strains. The locus is situated in the middle of chromosome 2, and an allele from one of the eight strains swept to very high frequencies in the set of mice generated by the intercrosses (Didion et al. 2015). That allele would undoubtedly have gone to fixation in the set of mice if the crosses had not been reorganised to minimise its impact. The cheater allele ($R2d2^{HC}$ – where the *HC* stands for 'high copy number') has a 127 kb unit repeated about 36 times, and may form a neocentromere promoting meiotic drive at metaphase II, in a similar way to the maize neocentromere (Didion et al. 2015; Zanders and Malik 2015). The alleles in other inbred strains either have no repeats at the *R2d2* locus or only have a small number of repeats, and so they would not organise a neocentromere. As is commonly observed in other meiotic drive systems (Zanders and Unckless 2019), the $R2d2^{HC}$ allele in the heterozygous state is associated with reduced fertility as well as meiotic drive (Didion et al. 2015), but this did not stop the allele increase towards fixation in a laboratory situation. The $R2d2^{HC}$ allele is also found in wild populations in western Europe and eastern North America but it is not fixed (Didion et al. 2016). The counteracting fertility cost shown in $R2d2^{HC}$ heterozygotes may be part of the reason why the $R2d2^{HC}$ allele is present in a polymorphic rather than a fixed state. Another possibility is the presence of drive suppression in the natural populations. The nature of such a suppressor or suppressors can only be speculated on, but while cheating may be advantageous for the cheater allele, alleles at other loci are expected to oppose it (Fishman and McIntosh 2019), and suppression is very widely observed in meiotic drive systems and can evolve rapidly (Lindholm et al. 2016). It is notable that in crosses among laboratory mouse strains the $R2d2^{HC}$ allele does not show biased transmission on all genetic backgrounds (Didion et al. 2015), providing further reason to think that drive suppression could be present or could evolve in natural populations as well. Studies by Finseth et al. (2021) on yellow monkeyflower (*Mimulus guttatus*) reveal such a situation of a true meiotic drive system impacted by drive suppression, generating polymorphism for the cheater allele rather than complete fixation. The monkeyflower model represents a particularly clear example of a co-evolutionary arms race between a centromeric region exhibiting meiotic drive and an unlinked modifier locus that codes a centromeric protein that suppresses drive.

The selective modification of centromeric proteins promoting drive suppression was actually already incorporated into the centromere drive model of Henikoff et al. (2001). They further posited that the arms race between the driving centromeres and unlinked modifier loci within populations could also lead to incompatibilities between populations (diverging centromeric systems associated with hybrid defects). In this way, they argue that meiotic drive could contribute to the speciation process.

The centromere drive model of Henikoff et al. (2001) has recently been extended by Kumon et al. (2021) based on their experimental studies and evolutionary analysis in the Murinae (the subfamily including the house mouse). A new model proposed by Kumon et al. (2021) incorporates roles for centromeric sequences and centromeric proteins but also heterochromatin proteins (prevalent in regions flanking centromeres), which can contribute to drive suppression.

Returning to White's (1968) hypothesis that true meiotic drive is important to explain the fixation of chromosomal rearrangements: The chromosomal rearrangements that would have the highest potential to show meiotic drive are those that involve the centromeric region in the rearrangement. Through changes to the centromeric region the rearrangements may influence the centromere, including properties such as its size, which may cause the rearrangement to show greater transmission than the ancestral condition in heterozygotes. The rearrangements concerned are Robertsonian fusions (whereby telocentrics–chromosomes with terminal centromeres–fuse at their centromeric regions to form metacentrics–chromosomes with distinctly internal centromeres), Robertsonian fissions (the reverse process), whole-arm reciprocal translocations (where metacentric chromosomes swap whole chromosome arms with other metacentrics or with telocentrics, again involving breakages in the centromeric regions), pericentric inversions and centric shifts. Interesting for all these rearrangements, there are lineages where the same type of rearrangement has arisen and become fixed repeatedly, a phenomenon that has been termed 'karyotypic orthoselection' (White 1973). For example, centric shifts have occurred repeatedly in rock-wallabies *Petrogale* (Potter et al. 2017), whole-arm reciprocal translocations have occurred repeatedly in common shrews *Sorex araneus* (White et al. 2010) and pericentric inversions have occurred repeatedly in deer mice *Peromyscus* (Robbins and Baker 1981). The repeated occurrence of the same type of rearrangement, clearly reflects a propensity for the same type of mutation. However, there is still a necessity for fixation, and true meiotic drive may explain that. Thus,

the centromeres may be affected in similar ways by the chromosomal mutations that repeatedly occur in certain lineages and have a similar transmission advantage. This idea has been developed further by Pardo-Manuel de Villena and Sapienza (2001). They noticed that mammalian karyotypes have a greater tendency than expected to be either fully metacentric or fully telocentric. This is presumably driven by repeated occurrence and fixation of either Robertsonian fusions or Robertsonian fissions respectively. The house mouse shows repeated occurrence of Robertsonian fusions in one species, with about 100 geographically-limited populations (also termed chromosomal races) each characterised by a particular karyotype with 1–9 pairs of fusions (Piálek et al. 2005; Garagna et al. 2014). The work by Chmátal et al. (2014) showing centromere drive in house mice, was based on comparisons of metacentrics and telocentrics in this species. This centromere drive model, based on large vs. small centromeres, therefore provides a mechanism for the true meiotic drive predicted by Pardo-Manuel de Villena and Sapienza (2001) to explain the biased distribution of karyotypes in mammals.

Having pointed out the possibility that chromosomal rearrangements that cause a perturbation of the centromeric region may be particularly prone to meiotic drive, that does not rule out other types of association of chromosomal rearrangements and meiotic drive. As always, there is need for careful study to establish cause and effect. If rearrangements of a particular type occur frequently, and if centromeric drive also occurs frequently, then by chance a particular rearrangement could be linked to a driving centromere. In this way a chromosomal rearrangement could become fixed without the rearrangement itself promoting drive.

Meiotic drive is not the only possible process that promotes fixation of chromosomal rearrangements. Well-argued alternatives are genetic drift (Lande 1979; Coyne 1989) and the selective advantage of bringing together locally adapted loci in close linkage (Guerrero and Kirkpatrick 2014). These explanations fit best for small populations (genetic drift) or populations in small geographic areas (local adaptation). It is interesting that the individual chromosomal races of the house mouse described above have small distributions, and that is true of other situations where species display multiple chromosomal forms (Searle 1993). However, the alternatives of meiotic drive/suppression of meiotic drive that has been described above to explain the occurrence of within population polymorphism, may also explain the patchy distribution of chromosomal forms in species such as the house mouse, with meiotic drive able to occur in areas where there is not suppression, but be blocked from areas where there is suppression. Thus, 'local meiotic drive' can also explain chromosomal forms having limited distributions within species (Garagna et al. 2014). Whether it is meiotic drive or another factor or multiple factors that explains the occurrence of local chromosomal forms, the occurrence of those geographically-limited entities can scale up to between species variation in karyotype, because range contractions and expansions, due for instance to climate oscillations, can lead forms with small ranges to have much larger ranges. And forms with previously large ranges (e.g. with the ancestral karyotype) can go extinct. Also, the type of accumulation of chromosomal rearrangements seen, for instance, in the house mouse (where there are populations characterised by up to 9 Robertsonian fusions: Piálek et al. 2005), can result in a new chromosomal form which, on chromosomal grounds, would show low fertility on hybridisation (errors in chromosome pairing and segregation in hybrids) with any other extant population. This may also enhance the speciation process.

It is appropriate to be thinking about meiotic drive on the 200th anniversary of Gregor Mendel's birth. It was his laws that laid the foundation for our understanding of inheritance. In 1908, less than a decade after the rediscovery of Mendel's findings, the most prominent early Mendelist, William Bateson, said: "Treasure your exceptions! When there are none, the work gets so dull that no one cares to carry it further. Keep them always uncovered and in sight. Exceptions are like the rough brickwork of a growing building which tells that there is more to come and shows where the next construction is to be." (Carlson 1985). The phenomenon of meiotic drive will keep studies of inheritance from being dull for many years to come!

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AUTHOR CONTRIBUTIONS

JBS and FPMV conceived and worked on the paper. Both authors approve the final version.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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