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PERSPECTIVE

Inbreeding, male viability, and the remarkable evolutionary stability of the aphid X chromosome

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Aphids exhibit an atypical XX/X0 sex determination system in which rare X0 males are produced when XX individuals undergo programmed loss of a randomly chosen X chromosome. Two recent studies revealed at least 30 million years of nearly total stability of the aphid X chromosome gene complement in the face of dramatic rearrangements of autosomes. I note that a lack of X chromosome turnover could be in part due to the unusually large effects on gene dosage for X-autosome fusions under somatic X chromosome loss. While these dynamics predict stasis under intensive inbreeding, a condition likely to hold for most aphids, more complex dynamics are expected under outbreeding. These more complex dynamics are discussed in light of potential associations with population extinction and parthenogenesis. I discuss additional potential contributors to X chromosomal stasis including problems with spermatogenesis or male production and gene dosage effects. I conclude by discussing future directions and connections to other systems.

Sex chromosome evolution in aphids and other animals

Sex chromosomes show remarkably diverse evolutionary histories across animals. In many lineages, neo-sex chromosomes frequently arise, either through evolution of a novel sex determination locus, movement of the ancestral sex determination locus to a new chromosome, or, perhaps most commonly, through fusion of an autosome to a pre-existing sex chromosomes ("X-autosome fusions"; Bachtrog et al. 2014). According to the most influential model, sex chromosome-autosomal fusions are driven by autosomal alleles that are beneficial in one sex but costly in the other, with fusions of such "sexually antagonistic" alleles to sex chromosomes allowing them to be more commonly inherited through the sex in which they provide a benefit (Charlesworth et al. 2005; Van Doorn and Kirkpatrick 2007). In particular, alleles that are beneficial in females but costly in males may benefit from becoming linked to the X chromosome, which is inherited from females two-thirds of the time on average. For instance, in jumping spiders, there is a clear overrepresentation of fusions involving the X chromosome (Maddison and Leduc-Robert 2013). Other models envision a role for meiotic drive, dynamic interactions with sex ratio distorting symbionts, or other forces (e.g., Yoshida and Kitano 2012; Furman et al. 2020). In some cases, recurrent fusions have led to chains of sex chromosomes, leading to cases such as termites in which the majority of genes are sex-linked (Charlesworth and Wall 1999; Vincke and Tilquin 1978).

At the other end of the spectrum, two recent studies reported the case of aphids (Mathers et al. 2020a; Li et al. 2020). Studying chromosome-level assemblies of multiple aphid species, the authors reported a striking deficit of X chromosomal turnover—whereas autosomes have undergone enough rearrangement as to essentially scramble chromosome-level linkage, more than 95% of X-linked genes show conserved X-linkage across species, indicating a nearly complete absence of gene movement or X-autosomal fusions for at least 30 million years of aphid evolution.

Cyclic parthenogenesis and sexual antagonism

It is suggestive that this remarkable X chromosomal stasis is found in species with other equally remarkable aspects of X chromosomal biology (Dixon 1977). Aphids' atypical

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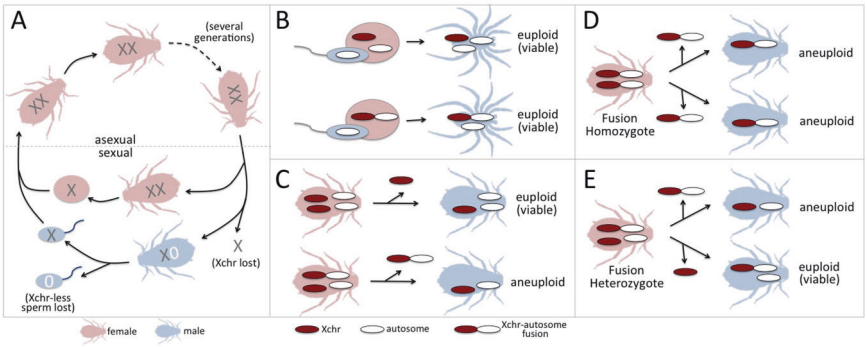

Fig. 1 Elevated effects of X chromosome-autosome fusion on gene dosage in aphids. A Life cycle of pea aphids. In contrast to most generations, which are asexual and all-female (top), sexual generations involve parthenogenetically produced females and males, the latter produced by random loss of one X chromosome. X chromosome drive in males produces all X-bearing sperm, thus fertilization leads again to XX females. **B** In standard XX/X0 systems, X-autosome fusion (bottom) does not change gene complement in males relative to the non-fused condition (top). **C** In the aphid system, X-autosome fusion (bottom) can lead to changes in gene complement in males (aneuploidy) relative to the unfused condition (top), which occurs when the fused chromosome is eliminated. **D** In females homozygous for the chromosomal fusion, all sons have nonstandard gene complements (aneuploid) and thus may not be viable, possibly leading to inviability of all sons and mating limitation for daughters in the case of sibmating. **E** In females heterozygous for the chromosomal fusion, sons that eliminate the fused chromosome have nonstandard gene complements, perhaps leading to an advantage for sons that retain the fused chromosome.

X chromosome biology is related to the phenomenon of so-called cyclic parthenogenesis, which is found in most aphid species. Under aphid cyclic parthenogenesis, most generations consist exclusively of asexually produced daughters; occasional sexual generations occur through asexual production of sons and daughters, who then mate to sexually produce the next generation of asexual daughters. Sexual generations occur only rarely and usually seasonally (most commonly in the autumn; Fig. 1A; Dixon 1977). Consistent with an XX/X0 sex determination system, both asexual and sexual females carry two X chromosomes per cell, while X0 males are produced by loss of one randomly chosen X chromosome at the one-cell stage. The X chromosome then undergoes meiotic drive during spermatogenesis to produce all X-bearing sperm. Mating of X0 males with XX females thus produces only XX females (Wilson et al. 1997).

Notably, this atypical biology predicts a reduction in the incidence of X-autosome fusions relative to standard systems. For standard X chromosomes, the fact that some sperm do not contain an X chromosome implies that the X chromosome experiences female-biased transmission relative to autosomes (which are present in all euploid gametes). As a consequence, mutations that are particularly beneficial in females are expected to benefit from being X-linked; occurrence of such female-beneficial mutations on autosomes could drive X-autosomal fusion (as noted above). By contrast, the aphid X chromosome is not expected to be inherited through females more frequently than autosomes: all sperm, like all eggs, carry X chromosomes, thus the X is expected to be inherited through males only the same (small) fraction of time as are autosomes (Jaquiéry et al. 2012, 2013). As such, in the absence of dominance (i.e., heterozygote fitness is the average of that of the two homozygotes), mutations that are particularly beneficial in females are not expected to benefit from being X-linked, potentially eliminating a strong force driving X-autosomal fusion. However, while these considerations suggest an explanation for why the aphid X might not be particularly prone to fusions, it does not explain why the aphid X might be particular resistant to fusion.

Consequences of X-autosome fusion under X chromosome loss

The striking bias away from X-autosome fusions in aphids could be in part explained by the unique effects of X-autosomal fusion on gene dosage in aphids. This may be seen by comparing the case for standard and aphid X chromosomes. For X chromosomes in most systems (but not aphids), X-autosome fusions are not expected to lead to immediate large-scale effects of altered gene copy number (one allele instead of two; Fig. 1B). Instead, genes within the newly X-linked region remains present in two copies. Over time, newly sex-linked sequences do experience Y chromosomal degradation, leading to dosage difference between males and females; however, because this process is not immediate, there is time for compensatory changes to accommodate or rebalance gene expression in the face of differences in copy number (Zhou et al. 2013; Vicoso and Bachtrog 2009).

The case for X-autosomal fusions in aphids is quite different (Fig. 1C). For an X-autosome fusion, X chromosomal loss to yield X0 males would now presumably entail loss of the entire fused chromosome, leading immediately

to gene expression problems in males, with the gene complement of an entire autosome now quite suddenly being present in only one copy. Such chromosomal aneuploidies tend to be quite deleterious and often lethal in animals (Santaguida and Amon 2015). Thus, X-autosomal fusion in aphids is expected to have much more drastic immediate consequences than for standard X chromosomes.

Dynamics of aphid X-autosome fusions under inbreeding and outbreeding

Notably, the consequences of these dynamics are expected to be quite different under inbreeding and outbreeding. Many aphids show high levels of inbreeding, largely due to mating between asexually produced siblings, leading to high levels of homozygosity. (Consistent with this notion, many aphids show female-biased sex ratios, often associated with inbreeding; Foster 2002.) For females that are homozygous for the fusion, all sons are expected to perish, which may additionally reduce the fitness of daughters insofar as they are dependent for mating on the presence of viable sons. Thus inbred families bearing X-autosome fusions could have low fitness, explaining the lack of observed X-autosome fusions in inbred aphids (Fig. 1D).

However, this explanation is complicated by evidence that some aphids are not thought to undergo regular sibling mating. For instance, signatures of regular outcrossing have been found in *Sitobion avenae* and in *Myzus cerasi* (Papura et al. 2003; Mathers et al. 2020b). Under outbreeding, we might even expect the fused chromosome to have an advantage. Under random mating, a rare allele is primarily present in heterozygotes. For mothers heterozygous for an X-autosomal fusion, only sons that lack the fused chromosome would be expected to perish (Fig. 1E). Thus the fused chromosome could stand to benefit if there is competition between relatives: in particular, in the case of a sexual generation produced from an asexual female that is heterozygous for the fusion, both fusion-bearing X0 males as well as heterozygous daughters could benefit from the inviability of the fused chromosome-eliminating X0 males. The lack of observed X-autosomal fusions in outbred species thus requires further investigation.

Dynamics of aphid X-autosome fusions under complex mating systems

One possibility is that, under certain circumstances, even a small amount of inbreeding may suffice to prevent X-autosomal fusion from invading the population. For a simple model (see Appendix for details), in which male zygotes are produced at a rate m, and in which a fraction b of resources from inviable males are reallocated to production of additional offspring, and in which a fraction F of sexual offspring are homozygous due to inbreeding (i.e., F is equal to the probability that an offspring's two alleles are IBD), a rare fusion chromosome will have lower fitness than wildtype when $F > mb/(1 - m/2 - m^2b/2)$. Notably, this model remains incomplete, and factors that are not considered include inbreeding depression and facultative sex allocation. Each of these factors could increase the advantage in heterozygotes relative to the disadvantage in homozygotes and thus increase the degree of inbreeding required to prevent invasion of an X-autosome fusion. Nonetheless, these considerations suggest that under certain assumptions, low F can be sufficient to avoid invasion of the chromosome, so long as mb, the total fraction of resources reallocated, is low, which is to say inefficient reallocation b and/or a low fraction of progeny being inviable males (Fig. 2).

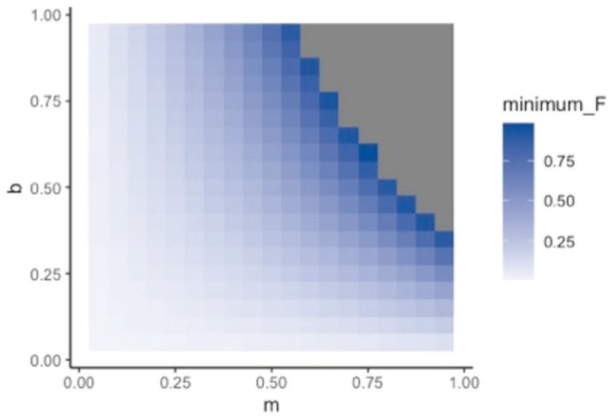

Fig. 2 Minimum F values at which invasion of an X-autosome fusion is prevented, representing the derived equation $F > mb/(1 - m/2 - m^2b/2)$. As expected from the numerator mb, low values of F can prevent invasion when reallocation of resources is low due either to a small fraction of males (low m) or a low rate of reallocation (b).

Two considerations suggest that it is possible that such conditions hold in the vast majority of aphids. First, reallocation may not be efficient if food availability is not limiting (in which case cannibalism of inviable sibling eggs may not substantially increase fitness), a condition that seems plausible in many aphids insofar as food sources from sap, etc., may be abundant (e.g., Moran 1992). Moreover, many aphid species have female-skewed sex ratios ($m < 0.5$) (Foster 2002), which is consistent with substantial inbreeding occurring across a diversity of aphids (90% of aphid species being estimated to have female-biased sex ratios, often associated with inbreeding). Notably, low m also reduces the degree of inbreeding sufficient to prevent invasion of an X-autosome fusion (see preceding paragraph).

However, the diversity of aphid lifestyles makes it far from certain that inbreeding alone would have been

sufficient to explain the lack of fusions throughout the long evolutionary histories over which X-autosome fusions have been rare. In particular, in aphid species that alternate between hosts (~10% of species), sexual individuals often migrate prior to mating, seemingly reducing the opportunity for inbreeding (e.g., Dixon 1977; Dixon and Kundu 1994). Consistent with lack of frequent sibling mating, signatures of regular outbreeding (high levels of heterozygosity, low linkage disequilibrium) have been found in such species (Papura et al. 2003; Mathers et al. 2020b). Previous work has shown that the complex history of aphid lifecycles make it difficult to reconstruct specific transitions through evolutionary time; however, clear evidence for frequent transitions between different lifecycles urges caution in assuming constant inbreeding over long evolutionary times (e.g., Moran 1992).

Extended dynamics under outbreeding

Could other forces explain a lack of X-autosome fusions under outbreeding? Notably, whereas under inbreeding selection against fusions is expected, under outbreeding the dynamics are expected to be considerably more complicated. Notably, because the fraction of males killed is linearly dependent on the number of copies of the fused chromosome in the population, as a fusion spreads in an outbred population, males become increasingly rare. Moreover, as the fusion spreads, homozygous wildtype females become rarer, a process that is self-catalyzing because only homozygous wildtype females produce wildtype sons, which are necessary to sire the next generation of homozygous wildtype individuals. As a consequence, sex ratios quickly become radically skewed, likely leading to problems for females in finding mates. Even for moderate values of m and b, this process is expected to be remarkably fast—for instance, for a starting frequency of the fusion of 0.001, with $m = 0.3$ and $b = 0.2$, the sex ratio skews to 95% females within 246 generations (see "Methods") in an infinite population. For $m = 0.5$ and $b = 0.5$, it takes only 59 generations (Fig. 3). It is interesting to speculate on the fate of such populations. If these populations are not rapidly driven to extinction, two possibilities present themselves. First, females could evolve a strong preference for wildtype males, although if most females are already homozygous for the fusion, the effect of such a preference is limited since heterozygous daughters will not produce wildtype grandsons. Perhaps a more likely outcome is the loss of sexual reproduction altogether, which is observed in many lineages of aphids (Moran 1992; Simon et al. 2002). It will be interesting to characterize X-autosomal fusion in parthenogenetic aphids.

Collectively, these thoughts suggest a more complex story. While dosage-based considerations do predict resistance to X-autosomal fusions in many inbred aphid lineages, if a dearth of X-autosomal fusions in truly outbred aphid lineages is found, this will suggest that dosage is not the entire picture. Other possibilities arising from peculiarities of molecular mechanism are imaginable, including problems with programmed X chromosomal loss in females heterozygous for a fusion, problems with X-autosome fusions in spermatogenesis (particularly the requirement that all sperm bear the X chromosome), or problems with dosage compensation in males with chromosomal fusions (for instance, misexpression of genes on the fused autosomes). However, while these possibilities are imaginable it is not clear why they should be expected to be consistent across eons of evolution, since there is no clear logical reason why they should be inevitable (and thus evolutionarily consant). Conceivably, the full answer lies in a combination of factors, each reducing the probability that an X-autosomal fusion will arise, with contributions for dosage problems in inbred lineages, dosage problems for fused chromosomes, problems with X chromosome loss, and other unimagined mechanistic problems collectively causing successful X-autosomal fusions to be rare, and potentially with extinction or evolution of obligate asexuality (perhaps eventually followed by extinction) in those rare lineages that do evolve a successful fusion.

Concluding remarks

The above considerations suggest a partial explanation for the deep stasis of X chromosomal complement in aphids. Regardless of the explanation, Mathers, Li and coauthors' findings add to the growing list of striking properties of the aphid X chromosome, from somatic loss to germline drive to differences in sex biases in expression patterns. It will be of particular interest to characterize X chromosomes from

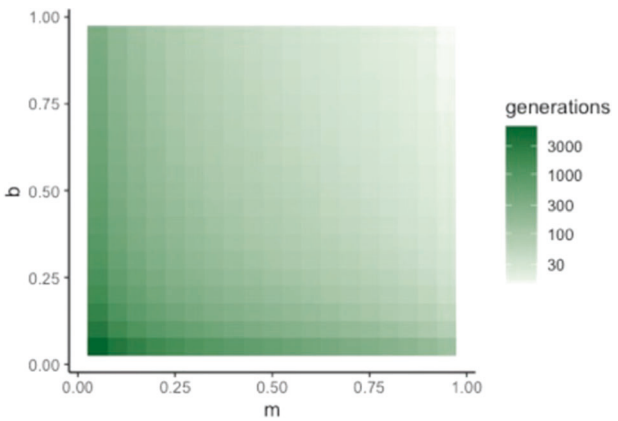

Fig. 3 Number of generations for invasion of a X-autosomal fusion for various values of m and b, assuming no inbreeding ($F = 0$). Shown is the expected number of generations until the sex ratio reaches 99% males, beginning with frequency 0.01 of the fused chromosome, in an infinite population. Note that m represents the fraction of male zygotes produced by females.

Table 1 Expected values for quantities under the model described.

Maternal genotype	WT	Fusion heterozygote		Fusion homozygote
Approximate frequency when $p << 1$	$1-p$	$2p(1-F)$		$p(1-F)$
Focal chromosome	Unfused	Unfused	Fused	Fused
Relative number of sons bearing the focal chromosome	$m/2$	0	$(m/2)\times[1+b\times m/2/(1-m/2)]$	0
Average male fitness	$0.5/m$	$0.5/m$	$0.5/m$	$0.5/m$
Fraction of sperm bearing focal chromosome	1	1	1	1
Total male fitness for focal chromosome	0.25	0	$0.25\times[1+b\times m/2/(1-m/2)]$	0
Relative number of females (all bear focal chromosome)	$1-m$	$(1-m)\times[1+\mathrm{b}\times m/2/(1-m/2)]$	$(1-m)\times[1+b\times m/2/(1-m/2)]$	$1-m$
Average female fitness	$0.5/(1-m)$	$0.5/(1-m)$	$0.5/(1-m)$	$0.5/(1-m)$
Fraction of eggs bearing focal chromosome	0.5	0.5	0.5	0.5
Total female fitness for focal chromosome	0.25	$0.25\times[1+b\times m/2/(1-m/2)]$	$0.25\times[1+\mathrm{b}\times m/2/(1-m/2)]$	$0.25\times(1+mb)$
Total fitness for focal chromosome	0.5	$0.25\times[1+b\times m/2/(1-m/2)]$	$0.5\times[1+b\times m/2/(1-m/2)]$	$0.25\times(1+mb)$
Relative frequency	$1-p(2-F)$	$p(1-F)$	$p(1-F)$	pF

aphids with long-standing outbreeding mating patterns as well as from fully asexual lineages. It will also be interesting to learn how such dynamics play out in other atypical systems, including other lineages with different mechanisms of male production by X chromosomal loss (Goday and Esteban 2001; Haig 1993; Benatti et al. 2010). In addition, it is interesting to consider the potential relevance to other systems with less systematic production of X0 males by X chromosome loss (e.g., *Caenorhabditis elegans*), as well as other instances of long-term stability of X chromosome gene content (e.g., mammals; Delgado et al. 2009; Zhou et al. 2008). These results underscore the importance of characterizing atypical genetic systems to broaden our understanding of the evolutionary forces driving genome dynamics in all organisms.

Methods

Population invasion under outbreeding

An individual-based simulation was run for various m and b values, beginning with a frequency of the fused chromosome of 0.001. In each sexual generation, expected male and female production was tabulated across each maternal and the expected frequencies of different sexually produced genotypes tabulated under random mating. The simulation was run until the sex ratio reached >99% females, and number of generations required recorded.

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Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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Appendix: A simple model for selection on an X-autosome fusion

Let m represent the fraction of offspring that are males. Let b represent resource allocation, that is, the fraction of resources from an inviable offspring that are reallocated to increased fitness of siblings. Assume that the sex ratio of the offspring produced from these reallocated resources is the same as for all offspring (namely, a fraction m males). Let F represent the fraction of sexually produced offspring that are homozygous at a given locus due to inbreeding. Assume equal fitness of inbred and outbred individuals. We can then calculate the brood fitness (that is, the total fitness of all offspring of a given mother) as well as the chromosomal fitness (the brood fitness weighted across offspring by 0.5 for heterozygotes and 1 for homozygotes and male), as shown in Table 1. Note that, as expected, the fitness for the fused chromosome is higher than wildtype (unfused) in heterozygotes (due to reallocation of resources from males lacking the fused chromosome to offspring bearing the fused chromosome), but lower than wildtype in homozygotes (due to overall decrease in offspring production due to male inviability). The fused chromosome is not expected to invade the population when the weighted average chromosomal fitness is lower than that of wildtype, namely:

$$0.5\times[1+b/(1-m/2)]\times(1-F)+0.25\times(1+mb)\times F<0.5,$$ which simplifies to

$$F>mb/\left(1-m/2-m^2b/2\right).$$

Cutoff values for F are shown in Fig. 2.

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