Genomic Imprinting Leads to Less Selectively Maintained Polymorphism on X Chromosomes

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ABSTRACT Population-genetic models are developed to investigate the consequences of viability selection at a diallelic X-linked locus subject to genomic imprinting. Under complete paternal-X inactivation, a stable polymorphism is possible under the same conditions as for paternal-autosome inactivation with differential selection on males and females. A necessary but not sufficient condition is that there is sexual conflict, with selection acting in opposite directions in males and females. In contrast, models of complete maternal-X inactivation never admit a stable polymorphism and alleles will either be fixed or lost from the population. Models of complete paternal-X inactivation are more complex than corresponding models of maternal-X inactivation, as inactivation of paternally derived X chromosomes in females screens these chromosomes from selection for a generation. We also demonstrate that polymorphism is possible for incomplete X inactivation, but that the parameter conditions are more restrictive than for complete paternal-X inactivation. Finally, we investigate the effects of recurrent mutation in our models and show that deleterious alleles in mutation–selection balance at imprinted X-linked loci are at frequencies rather similar to those with corresponding selection pressures and mutation rates at unimprinted loci. Overall, our results add to the reasons for expecting less selectively maintained allelic variation on X chromosomes.

A gene is said to be imprinted when its level of expression is dependent on the parent from which it was inherited. Imprinted loci are characterized by the reduced or nonexpression of either the paternally or maternally derived allele at a particular developmental stage or in a specific tissue type (Reik and Walter 2001). Complete inactivation of an imprinted gene results in functional haploidy, with only one of the two copies of a gene expressed. A well-characterized example of an imprinted gene is insulin-like growth factor II in mice (*Igf2*) and humans (*IGF2*)—in most tissues the maternally derived copy of the gene is inactive and only the paternally derived copy is expressed (DeChiara *et al.* 1991; Giannoukakis *et al.* 1993). To date, 250 imprinted genes have been identified in mammals, including 73 in humans, and many of these genes are thought to be involved in traits such as growth and development (Morison *et al.* 2005).

A number of studies have demonstrated that genomic imprinting and imprinting-like phenomena may also occur at X-linked loci. It is worth noting that X chromosome inactivation in marsupials and in some tissues of other mammals is formally equivalent to standard single-locus genomic imprinting, since expression or nonexpression of an allele at an X-linked locus is dependent on the parent from which it was inherited. In addition to the well-known examples of paternal-X inactivation in extraembryonic membranes of some eutherian females, including mice, rats, and cattle (Takagi and Sasaki 1975; Wake *et al.* 1976; West *et al.* 1977; Harper *et al.* 1982; Xue *et al.* 2002; Wagschal and Feil 2006), in preimplantation rodent embryos (Latham 2005) and somatic tissues of kangaroos and other marsupials (Sharman 1971; Graves 1996, Johnston *et al.* 2002), there is also evidence of such phenomena in the somatic tissues of eutherian mammals. Preferential inactivation of the maternally derived X chromosome (rather than the usual pattern of random inactivation; Graves 1996) has been observed in the somatic cells of female mice (Cattanach and Perez 1970; Falconer and Isaacson 1972; Falconer *et al.* 1982). More circumstantially, Hunt (1991) demonstrated that the viability of female mice with only one X chromosome was lower in mice whose X chromosome was paternally derived,

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suggesting that a number of genes relating to fitness may be expressed exclusively from the maternally inherited X chromosome. In addition, mice inheriting only a paternal X chromosome show developmental retardation in early organogenesis, whereas mice with a maternally inherited X chromosome develop normally (Thornhill and Burgoyne 1993; Jamieson *et al.* 1998). Kay *et al.* (1994) established that the *Xist* gene, which influences X inactivation and is located on the long arm of the X chromosome, is imprinted in mice. Female embryos initially express only the paternal *Xist* allele, but later allele expression is random with respect to parental origin.

Studies of Turner syndrome in humans, a disorder of females in which all or part of one X chromosome is deleted (Jacobs *et al.* 1990), provide growing evidence of imprinting at one or more loci on the human X chromosome (Knickmeyer 2012). For example, in a group with only one X chromosome, social adjustment was significantly better in individuals whose chromosome was paternally derived (Skuse *et al.* 1997), suggesting that a locus (or loci) for social cognition may be inactivated on maternally derived X chromosomes. Further, Bishop *et al.* (2000) found a significant difference in patterns of memory function between individuals whose only X chromosome was paternally derived and those whose X chromosome was maternally derived. This result suggests that there are one or more imprinted genes on the X chromosome that affect memory function (but see Ross *et al.* 2006).

Six putative imprinted genes or gene clusters on the X chromosome are currently listed in the *Catalogue of Imprinted Genes* (Morison *et al.* 2005), with evidence for both paternal and maternal inactivation. While complete paternal X inactivation results in hemizyosity for both males and females, maternal X inactivation in both male and female offspring means that males lack expression of the gene, whereas maternal X inactivation in females allows only hemizyosity for both males (expression of the maternal allele) and females (expression of the paternal allele). A number of genes are completely maternally inactivated (for example, *MAP7D2* is expressed from the paternally derived alleles in adult human females and has very low levels of expression in males, suggesting inactivation of the maternal allele in both sexes; Niida and Yachie 2011). There is currently no evidence of female-limited maternal inactivation of genes on the X chromosome. Nevertheless, it is predicted that sexually dimorphic imprinting may play an important role in the resolution of intralocus sexual conflict (Day and Bonduriansky 2004; Bonduriansky and Chenoweth 2009).

To date, there has been limited investigation of the population genetics of sex-linked imprinting. Most current theoretical models focus on the evolutionary origin of X-linked imprinting (for example, Iwasa and Pomiankowski 2001; Spencer *et al.* 2004; Haig 2006; Seymour and Pomiankowski 2006). This article expands upon two population-genetic models for imprinting at a sex-linked locus, namely Cooper (1976), who derived equilibria under viability selec-

tion for complete paternal-X inactivation, and Seymour and Pomiankowski (2006), who, although focusing on the evolution of imprinting in the context of two models where selection favors different levels of gene expression in males and females, also derived equilibria and local stability conditions for a general model where each of the six possible genotypes may have a different fitness (see Table 1). Selection at X-linked loci is of general interest, for example, because sex chromosomes are thought to be particularly important in the generation of sexual dimorphism through sexually antagonistic selection (Mank 2009; Connallon and Clark 2010). Cooper's model of viability selection is extended to apply to two models of maternal-X inactivation, and the equilibrium conditions are derived. The models are extended to explicitly encompass incomplete inactivation; that is, imprinting is treated as a quantitative phenomenon, and the equilibrium allele frequencies, feasibility, and local stability conditions are shown to be equivalent to those of Seymour and Pomiankowski (2006). There is considerable evidence that parent-of-origin inactivation of alleles on the X chromosome is dependent on the developmental stage or tissue type (see, for example, the *Catalogue of Imprinted Genes*, Morison *et al.* 2005), and polymorphism in imprinting status (albeit often with restrictive conditions) has been predicted by a number of theoretical models (for example, Spencer *et al.* 2004; Haig 2006; Seymour and Pomiankowski 2006). In this context the effect of imprinting on viability selection can be treated as incomplete and quantitative in nature. In addition to the selection models, mutation–selection balance at an imprinted, sex-linked locus is also investigated and, for all systems, the feasibility and stability of equilibrium allele frequencies is determined. Finally, in the discussion, we contrast our selection and mutation–selection models for imprinting on the X chromosome with dominance on the X chromosome and with imprinting at an autosomal locus.

The Imprinting Models

We examine the frequencies of two alleles at a single X-linked locus subject to complete inactivation in viability selection and mutation–selection models. We make the standard Hardy–Weinberg assumptions of no genetic drift, no migration, separate generations, and, where appropriate, no mutation.

Consider two alleles, A_1 and A_2 , at a single locus on the X chromosome. Let p_f and p_m represent the frequency of A_1 in the gametes of females (f) and males (m). In females, the homozygotes A_1A_1 and A_2A_2 have phenotypes A_1 and A_2 respectively, while the phenotype of the heterozygotes is dependent on the genotype of the expressed X chromosome. Writing the maternally derived allele first, paternal inactivation means that A_1A_2 heterozygotes are phenotypically A_1 and A_2A_1 heterozygotes are phenotypically A_2 , and vice versa under maternal inactivation (see Table 1).

In the following we present the main results from the selection and selection–mutation models of X-linked imprinting.

Table 1 Frequencies and viabilities for the genotypes at a diallelic X chromosome locus, ($s, t \leq 1$, $0 \leq k_1, k_2, h \leq 1$, $w_i > 0$)

Genotype: Genotypic frequencies	Females				Males	
	A_1A_1 $p_f p_m$	A_1A_2 $p_f(1 - p_m)$	A_2A_1 $(1 - p_f)p_m$	A_2A_2 $(1 - p_f)(1 - p_m)$	A_1 p_f	A_2 $(1 - p_f)$
Viability: complete paternal inactivation (see Cooper 1976)	$1 - s$	$1 - s$	1	1	$1 - t$	1
Viability: complete maternal inactivation in female offspring only	$1 - s$	1	$1 - s$	1	$1 - t$	1
Viability: complete maternal inactivation in both male and female offspring	$1 - s$	1	$1 - s$	1	1	1
Viability: incomplete inactivation	$1 - s$	$1 - k_2s$	$1 - k_1s$	1	$1 - t$	1
Viability: dominance, no imprinting	$1 - s$	$1 - hs$	$1 - hs$	1	$1 - t$	1
Viability: general case (see Seymour and Pomiankowski 2006)	w_1	w_2	w_3	w_4	w_5	w_6

Full mathematical details are provided in supporting information, [File S1](#).

Selection models

Model 1A. Complete paternal X inactivation: Following Cooper (1976), let us assume that the paternally derived alleles are inactivated and that the A_1 phenotype has viability $(1 - s)$ in females and $(1 - t)$ in males, ($s, t \leq 1$) (Table 1). This framework allows the possibility of sexual conflict; when s and t differ the viability of the A_1 allele is different in the two sexes.

As Cooper (1976) showed, the recursion equations for allele frequencies are

$$\begin{aligned} p_f' &= 0.5 \left[1 + p_m - \frac{1 - p_f}{1 - p_f s} \right] \\ p_m' &= 1 - \frac{1 - p_f}{1 - p_f t}. \end{aligned} \quad (1)$$

This system affords three equilibrium allele frequencies (*i.e.*, frequencies at which $p_f' = p_f$ and $p_m' = p_m$), $\hat{p}_f = \hat{p}_m = 0$ and $\hat{p}_f = \hat{p}_m = 1$, corresponding respectively to loss and fixation of the A_1 allele in both sexes, and

$$\hat{p}_f = \frac{s + t}{2st}, \quad \hat{p}_m = \frac{(1 - t)(s + t)}{t(s - t)}. \quad (2)$$

This polymorphic equilibrium is biologically feasible (*i.e.*, $0 < \hat{p}_f, \hat{p}_m < 1$) provided $s + t < 0$ and $s + t - 2st > 0$.

Standard local stability analysis (examining the leading eigenvalue of the system of equations linearized around the equilibrium; see Edelstein-Keshet 1988) shows that the polymorphic equilibrium is locally stable whenever it is feasible

and, indeed, whenever both fixation equilibria are unstable (Table 2).

Moreover, since the entries of the Jacobian matrix, $\partial(p_f', p_m') / \partial(p_f, p_m)$, are nonnegative (see Karlin 1972), the polymorphic equilibrium is globally stable whenever it is locally stable. Thus, if $s + t < 0$ and $s + t - 2st > 0$ so that both fixation equilibria are unstable, allele frequencies will always converge to the polymorphic equilibrium, an outcome that requires that s and t are of opposite sign. Nevertheless, this condition ($st < 0$) is not sufficient (see Figure 1) and, indeed, when selection is weak in one sex, there is a limited range that the other selection coefficient may take for the polymorphic equilibrium to exist and be stable (Cooper 1976). Unless selection for the A_1 allele is markedly different in the two sexes, it is unlikely that a polymorphic equilibrium would be observed.

Model 1B. Complete maternal X inactivation, females only: We assume that the maternally derived alleles are inactivated (but only in female offspring) and again that the A_1 phenotype has viability $(1 - s)$ in females and $(1 - t)$ in males, ($s, t \leq 1$) (Table 1).

The recursion equations for allele frequencies are now

$$\begin{aligned} p_f' &= 0.5 \left[1 + p_f - \frac{1 - p_m}{1 - p_m s} \right] \\ p_m' &= 1 - \frac{1 - p_f}{1 - p_f t}. \end{aligned} \quad (3)$$

There are now just two equilibrium allele frequencies, $p_f = p_m = 0$ and $p_f = p_m = 1$, corresponding to loss and fixation of the A_1 allele in both sexes. The above procedure of Karlin (1972) shows one of these to be both locally and globally stable depending on the sign of $s + t - st$ (Table 2).

Table 2 Feasibility and stability conditions for equilibria under complete imprinting at a diallelic X chromosome locus, ($s, t \leq 1$)

Equilibrium	Paternal X inactivation	Maternal X inactivation, female offspring only	Maternal X inactivation, female and male offspring
$p_f = p_m = 0$ (fixation of A_2 allele)	$s + t > 0$	$s + t - st > 0$	$s > 0$
$p_f = (s + t)/2st$, $p_m = (1 - t)(s + t)/(t(s - t))$ (polymorphism)	$s + t < 0$ and $s + t - 2st > 0$	No internal equilibrium	No internal equilibrium
$p_f = p_m = 1$ (fixation of A_1 allele)	$s + t - 2st < 0$	$s + t - st < 0$	$s < 0$

Figure 1 Plot of the stability and feasibility conditions for the three equilibria possible for X-linked complete paternal inactivation: (1) $p_f = p_m = 0$, requiring $s + t > 0$, (2) $p_f = (s + t)/2st$, $p_m = (1 - t)(s + t)/(t(s - t))$, requiring $s + t < 0$ and $s + t - 2st > 0$, and (3) $p_f = p_m = 1$, requiring $s + t - 2st < 0$. Note that $s + t = 0$ and $s + t - 2st = 0$ represent the border between dark and light shading and the border between light shading and no shading, respectively.

Model 1C. Complete maternal X inactivation, males and females: We assume that the maternally derived alleles are inactivated in both male and female offspring and that the A_1 phenotype has viability $(1 - s)$ in females and there is no selection in males ($s \leq 1$) (Table 1).

The recursion equations for allele frequencies are now

$$p'_f = 0.5 \left[1 + p_f - \frac{1 - p_m}{1 - p_m s} \right], \quad (4)$$

$$p'_m = p_f$$

As expected given the absence of sexual conflict to maintain a polymorphic equilibrium, there are again just two equilibrium allele frequencies, $p_f = p_m = 0$ and $p_f = p_m = 1$, corresponding to loss and fixation of the A_1 allele in both sexes. The above procedure of Karlin (1972) shows one of these to be both locally and globally stable depending on the sign of s (Table 2).

Model 1D. Incomplete inactivation: A more general treatment is to let the expression of maternally and paternally derived X alleles differ, such that the viability of reciprocal heterozygotes is not equal and is intermediate between the viability of the two homozygotes. We define the viabilities as $(1 - s)$ for the A_1A_1 genotype, $(1 - k_2s)$ for the A_1A_2 genotype, $(1 - k_1s)$ for the A_2A_1 genotype, and 1 for the A_2A_2 genotype in females. The parameters

k_1 and k_2 take values between 0 and 1. When $k_1 = k_2$ there is no imprinting, when $k_1 = 1 - k_2$ there is no dominance, and when $k_1 = k_2 = 0.5$ there is no imprinting or dominance. We assume that there is some expression of the X chromosome allele in males, such that the viability is $(1 - t)$ for the A_1 genotype and 1 for the A_2 genotype (Table 1).

The recursion equations for allele frequencies are now

$$p'_f = 0.5 \left[1 - \frac{1 - p_f - p_m - p_f p_m s}{1 - s(k_1 p_m (1 - p_f) + k_2 p_f (1 - p_m) + p_f p_m)} \right]$$

$$p'_m = 1 - \frac{1 - p_f}{1 - t p_f}. \quad (5)$$

This system affords three equilibrium allele frequencies, $\hat{p}_f = \hat{p}_m = 0$ and $\hat{p}_f = \hat{p}_m = 1$, and the polymorphic equilibrium

$$\hat{p}_f = \frac{k_2 s + t + k_1 s (1 - t)}{2s((1 - t)(k_1 - 1) + k_2)},$$

$$\hat{p}_m = \frac{(1 - t)(s(k_1 + k_2) + t - k_1 s t)}{2s(-1 + k_1 + k_2) + st(2 - k_2 - 3k_1) + t^2(-1 + k_1 s)}, \quad (6)$$

which is equivalent to (2) when $k_1 = 0$ and $k_2 = 1$. The polymorphic equilibrium is feasible provided $s((-2 + k_1)(1 - t) + k_2) - t < 0$ and $s(-k_1 - k_2 + k_1 t) - t > 0$. Seymour and Pomiankowski (2006) derived the recursion equations (see their Equation 2), polymorphic equilibrium (see their Equation A1), and local stability conditions (see their Appendix A) for the general case where all six genotypes (four in females and two in males, see Table 1) have separate viabilities; our recursion equations and equilibria above are, as expected, equivalent when the appropriate viabilities are substituted.

Mutation-selection models

We now incorporate recurrent mutation into models 1A–1D and investigate its effect on the above selectively maintained fixations. In particular, we investigate mutation from A_1 to A_2 when A_1 would otherwise be fixed by selection and from A_2 to A_1 when A_2 would otherwise be fixed by selection.

Model 2A(i). Complete paternal X inactivation, mutation from A_2 to A_1 : Suppose A_2 mutates to A_1 at a rate μ . The recursion equations are now

$$p'_f = p_f^s (1 - \mu) + \mu$$

$$p'_m = p_m^s (1 - \mu) + \mu,$$

in which p_f^s and p_m^s are p'_f and p'_m of (1), respectively.

The equilibria of the system are given by

$$\hat{p}_f = \mu \left[\frac{3}{s+t} \right] \text{ and } \hat{p}_m = \mu \left[\frac{3+s-2t}{s+t} \right], \quad (7)$$

$$\hat{p}_f = \frac{s+t}{2st} + \mu \left[\frac{2s^2 + t^2 - 3st}{2st(s+t)} \right]$$

and

$$\hat{p}_m = \frac{(1-t)(s+t)}{t(s-t)} + \mu \left[\frac{3s^2 - t^2 - 2s^2t + 4st^2 - 4st}{t(s+t)(s-t)} \right]$$

or

$$\hat{p}_f = \hat{p}_m = 1$$

with terms in μ^2 and above ignored.

The equilibrium of biological interest, (7), occurs when the fixation of A_2 is stable in Model 1 (i.e., when $s+t > 0$). Feasibility additionally requires $\mu < (s+t)/3$ whenever $t < s/2$ and $\mu < (s+t)/(3+s-2t)$ whenever $t > s/2$. By ignoring terms in μ^2 and above, approximate stability conditions for this equilibrium are $s+t > 0$ and

$$\mu < \frac{A(s+t)(A-s-3)}{A(s-1)(5s-t) + 3s + 10s^2 - 5s^3 - 15t - 10st + s^2t + 16t^2},$$

where $A = \sqrt{9-2s+s^2-8t}$. As expected, the mutation-selection balance given by (7) is feasible and stable when the pure selection A_2 fixation is feasible and stable, and mutation is sufficiently rare. Further, equilibria are globally stable wherever they are locally stable, provided μ is not large.

Model 2A(ii). Complete paternal X inactivation, mutation from A_1 to A_2 : We now consider the perturbation of the A_1 fixation by mutation. Let ν be the mutation rate from A_1 to A_2 . The recursions are now

$$p'_f = p_f^s(1-\nu) \\ p'_m = p_m^s(1-\nu).$$

Again, this system admits three equilibria, but the only one of biological interest is

$$\hat{p}_f = 1 - \nu \left[\frac{3(s-1)(t-1)}{2st-s-t} \right] \text{ and } \hat{p}_m = 1 - \nu \left[\frac{3+2st-4s-t}{2st-s-t} \right]. \quad (8)$$

This equilibrium is feasible provided $s+t-2st < 0$ (which ensures that the A_1 fixation is feasible and stable under pure selection), and $\nu < (2st-s-t)/(3(s-1)(t-1))$ whenever $t > s/(2-s)$ and $\nu < (2st-s-t)/(3-4s+2st-t)$ whenever $t < s/(2-s)$. By ignoring terms in ν^2 and above, approximate stability conditions for this equilibrium are $s+t-2st < 0$ and

$$\nu < \left(-2(2st-s-t)^2 \right) / \left[3s + 2s^2 + 3t - 15st + 2s^2t + t^2 + 4st^2 - \frac{(t-1)(-8s^3(1+t) + t(9+t) + s^2(4+38t) + s(9+t(4t-49)))}{\sqrt{(t-1)(-9+16s-8s^2+t)}} \right]$$

Provided mutation is rare, equilibria are globally stable wherever they are locally stable. Thus, the mutation-selection balance given by (8) is feasible and stable when the selection-only fixation of A_2 is feasible and stable and mutation is sufficiently rare.

Model 2B(i). Complete maternal X inactivation, females only, mutation from A_2 to A_1 : Again, suppose A_2 mutates to A_1 at a rate μ . The recursion equations are

$$p'_f = p_f^s(1-\mu) + \mu \\ p'_m = p_m^s(1-\mu) + \mu$$

in which p_f^s and p_m^s are p'_f and p'_m of (3), respectively. Under maternal-X inactivation, two equilibria are possible. The equilibrium of biological interest is

$$\hat{p}_f = \mu \left[\frac{3-s}{s+t-st} \right] \text{ and } \hat{p}_m = \mu \left[\frac{3-2t}{s+t-st} \right]$$

and represents the perturbation from fixation of the A_2 allele by mutation. It is feasible provided $s+t-st > 0$ (and so the fixation of A_2 under selection alone is stable), and $\mu < (s+t-st)/(3-2t)$ when $t > s/2$ and $\mu < (s+t-st)/(3-s)$ when $t < s/2$ (which means that mutation must be sufficiently rare). In addition, the local and global stability conditions require that

$$\mu < \frac{B(3-B)}{16(1-s)(1-t)-B-1},$$

where $B = \sqrt{1+8(1-s)(1-t)}$, ignoring terms in μ^2 and above.

Model 2B(ii). Complete maternal X inactivation, females only, mutation from A_1 to A_2 : Finally, we incorporate a mutation rate ν from A_1 to A_2 . The recursion equations are

$$p'_f = p_f^s(1-\nu) \\ p'_m = p_m^s(1-\nu)$$

and the equilibrium of biological relevance can be shown to be

$$\hat{p}_f = 1 - \nu \left[\frac{(2s-3)(t-1)}{st-s-t} \right] \text{ and } \hat{p}_m = 1 - \nu \left[\frac{(s-1)(t-3)}{st-s-t} \right].$$

This equilibrium, close to the selection only fixation of A_1 , is feasible provided $st-s-t > 0$ and $\nu < (st-s-t)/((2s-3)(t-1))$ when $t > s/(2-s)$ and $\nu < (st-s-t)/((s-1)(t-3))$ when $t < s/(2-s)$. Local and global stability conditions require that

$$\nu < \frac{C(3(1-s)(1-t)-C)}{(1-s)(1-t)(16-(s-1)(t-1)-C)},$$

where $C = \sqrt{(1-s)(1-t)(8+(1-s)(1-t))}$, ignoring terms in ν^2 and above.

Model 2C(i). Complete maternal X inactivation, males and females, mutation from A_2 to A_1 : Again, suppose A_2 mutates to A_1 at a rate μ . The recursion equations are

$$\begin{aligned} p'_f &= p_f^s(1 - \mu) + \mu \\ p'_m &= p_m^s(1 - \mu) + \mu, \end{aligned}$$

in which p'_f and p'_m are p'_f and p'_m of (4), respectively. Under maternal-X inactivation of both males and females, two equilibria are possible. The equilibrium of biological interest is

$$\hat{p}_f = \mu \left[\frac{3-s}{s} \right] \text{ and } \hat{p}_m = \mu \left[\frac{3}{s} \right]$$

and represents the perturbation from fixation of the A_2 allele by mutation. It is feasible provided that $s > 0$ (and so the fixation of A_2 under selection alone is stable) and $\mu < s/(3-s)$ (which means that mutation must be sufficiently rare). In addition, the local and global stability conditions require that

$$\mu < \frac{D(3-D)}{15-16s-D},$$

where $D = \sqrt{9-8s}$, ignoring terms in μ^2 and above.

Model 2C(ii). Complete maternal X inactivation, males and females, mutation from A_1 to A_2 : Finally, we incorporate a mutation rate ν from A_1 to A_2 . The recursion equations are

$$\begin{aligned} p'_f &= p_f^s(1 - \nu) \\ p'_m &= p_m^s(1 - \nu) \end{aligned}$$

and the equilibrium of biological relevance can be shown to be

$$\hat{p}_f = 1 - \nu \left[\frac{2s-3}{s} \right] \text{ and } \hat{p}_m = 1 - \nu \left[\frac{3(s-1)}{s} \right]$$

This equilibrium, close to the selection-only fixation of A_1 , is feasible provided that $s < 0$ and $\nu < s/(2s-3)$. Local and global stability conditions require that

$$\nu < \frac{E(3(1-s)-E)}{(1-s)(15+s-E)},$$

where $E = \sqrt{(1-s)(9-s)}$, ignoring terms in ν^2 and above.

Model 2D(i). Incomplete imprinting, mutation from A_2 to A_1 : Again, suppose A_2 mutates to A_1 at a rate μ . The recursion equations are

$$\begin{aligned} p'_f &= p_f^s(1 - \mu) + \mu \\ p'_m &= p_m^s(1 - \mu) + \mu, \end{aligned}$$

in which p'_f and p'_m are p'_f and p'_m of (5), respectively. Under maternal-X inactivation of both males and females, two equilibria are possible. The equilibrium of biological interest is

$$\hat{p}_f = \mu \left[\frac{3 - k_1 s}{s(k_1 + k_2) + t - k_1 s t} \right]$$

and

$$\hat{p}_m = \mu \left[\frac{3 + k_2 s - 2t}{s(k_1 + k_2) + t - k_1 s t} \right]$$

and represents the perturbation from fixation of the A_2 allele by mutation.

Model 2D(ii). Incomplete imprinting, mutation from A_1 to A_2 : Finally, we incorporate a mutation rate ν from A_1 to A_2 . The recursion equations are

$$\begin{aligned} p'_f &= p_f^s(1 - \nu) \\ p'_m &= p_m^s(1 - \nu) \end{aligned}$$

and the equilibrium of biological relevance can be shown to be

$$\hat{p}_f = 1 - \nu \left[\frac{(-3 + s(2 + k_2))(1 - t)}{s(2 - k_1 - k_2) + t - st(2 - k_1)} \right]$$

and

$$\hat{p}_m = 1 - \nu \left[\frac{-3 + s(4 - k_1) + t - st(2 - k_1)}{s(2 - k_1 - k_2) + t - st(2 - k_1)} \right].$$

Discussion

Our modeling reveals a critical difference between the effects of viability selection on complete paternal vs. maternal inactivation of X-linked loci: only the former can lead to a selectively maintained polymorphism. This difference arises because of the sexual asymmetry in the number of X chromosomes. Under paternal-X inactivation, the X chromosome derived from the father is hidden from selection for a generation when it is inactivated in his daughters. With maternal-X inactivation, by contrast, the paternal X is exposed to selection in daughters and the maternal X in sons, so that selection is effectively acting on a haploid system. We note that maintenance of allelic variation by viability selection on another naturally haploid system, Y chromosome loci, is also impossible (Clark 1987). Nevertheless, even under paternal inactivation, the conditions for the maintenance of polymorphism are restrictive. Not only must the selection coefficients act in opposing directions in the two sexes—that is, there is sexual conflict, such that the A_1 allele is beneficial in one sex but costly in the other—they must be of similar magnitude, especially when weak (Cooper 1976; see Figure 1). Intuitively, the maintenance of polymorphism requires not only that there is sexual conflict, but that the harm (*i.e.*, reduction in viability) in one sex is of similar magnitude to the benefit (*i.e.*, increase in viability) in the other. Imbalance in

the strength of selection between sexes means that either the A_1 or A_2 allele will be driven to fixation, as the costs to one sex outweigh the benefits to the other (or vice versa) (Rice 1984).

It is revealing to compare the equilibria under complete paternal-X inactivation with those under complete maternal autosomal inactivation with two sex viabilities (Pearce and Spencer 1992; Anderson and Spencer 1999). Following the convention of female and male viabilities being $(1 - s)$ and $(1 - t)$, respectively, we find that their three equilibria are equivalent to the three equilibria above, with both equilibrium frequencies for males and females and the selection coefficients s and t swapped (Table 3 and File S2). Further, the stability conditions for the maintenance of a stable internal polymorphism are the same, whereas conditions for the stability of each of the fixation equilibria are swapped (results not shown). This swapping is necessitated because the previous results concern maternal inactivation, whereas the X-linked polymorphism occurs only under paternal inactivation. Indeed, by deriving the equivalent paternal autosomal inactivation recursion equations to those in Pearce and Spencer (1992) and Anderson and Spencer (1999), we find that the equilibria (Table 3 and File S2) and stability conditions (results not shown) are identical to those under paternal-X inactivation.

This equivalence between autosomal and the X chromosome two-sex viability imprinting models contrasts with the lack of correspondence between nonimprinting models for differential male and female selection at autosomal and sex-linked loci (Owen 1953; Bennett 1957, 1958). Under standard Mendelian expression, two alleles in both males and females are exposed to selection on an autosome whereas two alleles in females and only one allele in males are exposed to selection at an X-linked locus. In both autosomal and sex-linked imprinting models, however, a single active chromosome is exposed to selection in both males and females. Nevertheless, although viability selection can maintain genetic variation at an unimprinted X-linked locus (Bennett 1957, 1958), the likelihood of such maintenance has been considered low, because, as in our imprinted case, the conditions, especially when selection is weak, are restrictive (Bennett 1958).

An interesting aspect in the general model of incomplete inactivation is whether a stable polymorphism is possible, and if so, the parameter space available for the polymorphism to be maintained. As shown in the results above, complete inactivation of the maternal X in females does not allow a stable polymorphism, despite the potential for selection to act in opposing directions in the two sexes. This lack of polymorphism is clear when examining the expression for equilibrium allele frequencies under incomplete inactivation in (6); when $k_1 = 1$ and $k_2 = 0$, the denominator for $\hat{p}_f$ is zero and the equilibrium allele frequency does not exist. This also occurs when $k_2 = (1 - t)(1 - k_1)$; assuming t is small (*i.e.*, selection is weak), polymorphism requires that the sum of k_1 and k_2 is not too close to 1. Further, by examining

Table 3 Comparison of equilibria for X-linked and autosomal imprinting with two sex viabilities, ($s, t \leq 1$)

X-linked paternal inactivation	$\hat{p}_f = \hat{p}_m = 0, \hat{p}_f = \hat{p}_m = 1$ and $\hat{p}_f = (s + t)/2st,$ $\hat{p}_m = (1 - t)(s + t)/(t(s - t))$
Autosomal maternal inactivation	$\hat{p}_f = p_m = 0, \hat{p}_f = \hat{p}_m = 1$ and $\hat{p}_f = (1 - s)(s + t)/(s(t - s)),$ $\hat{p}_m = (s + t)/2st$
Autosomal paternal inactivation	$\hat{p}_f = \hat{p}_m = 0, \hat{p}_f = \hat{p}_m = 1$ and $\hat{p}_f = (s + t)/2st,$ $\hat{p}_m = (1 - t)(s + t)/(t(s - t))$

the polymorphic equilibrium for incomplete imprinting (6), it can be seen that feasibility and stability conditions are the least restrictive for paternal-X inactivation and become more restrictive as the degree of inactivation tends toward maternal-X inactivation. For example, let $t = -0.1$. A polymorphic equilibrium is possible for s for a range of 0.017 ($0.083 < s < 0.1$) when $k_1 = 0$ and $k_2 = 1$, for a range of 0.011 ($0.086 < s < 0.097$) when $k_1 = 1/3$ and $k_2 = 2/3$, and for a range of 0.006 ($0.088 < s < 0.094$) when $k_1 = 2/3$ and $k_2 = 1/3$. Thus, everything else being equal, X-linked loci with incomplete inactivation are less likely to be variable than loci with complete paternal inactivation.

The incorporation of recurrent mutation into our viability selection models shows that disadvantageous alleles can be maintained at low mutation–selection balance frequencies. Unsurprisingly, these results require mutation to be rare and local stability of the selective fixation of the advantageous allele in the absence of mutation, conditions that also apply to most other models of mutation–selection balance. Mutation–selection balance at an X-linked locus was first examined by Nagylaki (1977). However, selection coefficients are not directly comparable to s and t in the above analyses, as Nagylaki (1977) derived equilibria in terms of average selection coefficients in males and females. To allow comparison in mutation–selection balance between X-linked loci with and without imprinting, we use Table 1 to derive recursion equations (see File S3) and hence find mutation–selection balance frequencies for $h = 0$, $h = 0.5$, and $h = 1$, where $(1 - hs)$ is the viability of the heterozygous females, and $h = 0$ implies complete dominance of the A_2 allele, $h = 0.5$ implies no dominance, and $h = 1$ implies complete recessivity of the A_2 allele. The recursion equations for allele frequencies in the absence of mutation are now

$$p'_f = 0.5 \left[1 - \frac{1 - p_f - p_m + sp_f p_m}{1 - sp_f p_m - hs(p_f + p_m - 2p_f p_m)} \right]$$

$$p'_m = 1 - \frac{1 - p_f}{1 - tp_f}$$

(see also Rice 1984). This system permits three equilibrium allele frequencies,

Table 4 Comparison of mutation-selection balance with and without imprinting at a sex-linked locus for mutation rate μ from A_2 to A_1 , ($s, t \leq 1$, $\mu > 0$)

	$\hat{p}_f$ (females)	$\hat{p}_m$ (males)	Feasibility condition	$(\hat{p}_f, \hat{p}_m)$ for $s = 0.1$, $t = 0.2$, $\mu = 10^{-5}$
Complete paternal X inactivation	$\mu \left[\frac{3}{s+t} \right]$	$\mu \left[\frac{3+s-2t}{s+t} \right]$	$s+t > 0$	$(10.0 \times 10^{-5}, 9.0 \times 10^{-5})$
Complete maternal X inactivation, female offspring only	$\mu \left[\frac{3-s}{s+t-st} \right]$	$\mu \left[\frac{3-2t}{s+t-st} \right]$	$s+t-st > 0$	$(10.4 \times 10^{-5}, 9.3 \times 10^{-5})$
Complete maternal X inactivation, male and female offspring	$\mu \left[\frac{3-s}{s} \right]$	$\mu \left[\frac{3}{s} \right]$	$s > 0$	$(29.0 \times 10^{-5}, 30.0 \times 10^{-5})$
No imprinting; $h = 0^a$	$\mu \left[\frac{3}{t} \right]$	$\mu \left[\frac{3-2t}{t} \right]$	$t > 0$	$(15.0 \times 10^{-5}, 13.0 \times 10^{-5})$
No imprinting and no dominance; $h = 0.5^a$	$\mu \left[\frac{6-s}{2s+2t-st} \right]$	$\mu \left[\frac{6+s-4t}{2s+2t-st} \right]$	$2s+2t-st > 0$	$(10.2 \times 10^{-5}, 9.1 \times 10^{-5})$
No imprinting; $h = 1^a$	$\mu \left[\frac{3-s}{2s+t-st} \right]$	$\mu \left[\frac{3+s-2t}{2s+t-st} \right]$	$2s+t-st > 0$	$(7.6 \times 10^{-5}, 7.1 \times 10^{-5})$

^a Where $(1 - hs)$ is the viability of the heterozygous females; see Table 1.

$$\hat{p}_f = \hat{p}_m = 0, \hat{p}_f = \hat{p}_m = 1,$$

$$\hat{p}_f = \frac{-2hs - t + hst}{2s(1 - 2h + ht - t)}, \hat{p}_m = \frac{(t-1)(-2hs + hst - t)}{s(h(t-2)^2 + 2(t-1)) - t^2} \quad (9)$$

The values for the polymorphic equilibria when $h = 0$, $h = 0.5$, and $h = 1$ are

$$(p_f, p_m) = \left(\frac{t}{2s(t-1)}, \frac{t(t-1)}{2s-2st+t^2} \right),$$

$$\left(\frac{2s+2t-st}{2st}, \frac{(t-1)(st-2s-2t)}{t^2(s-2)} \right) \text{ and}$$

$$\left(\frac{2s+t-st}{2s}, \frac{(t-1)(st-2s-t)}{2s-2st+st^2-t^2} \right),$$

respectively. In the absence of dominance ($h = 0.5$) the existence of the polymorphic equilibrium requires $st < 0$, $2s + 2t - 3st > 0$ and $2s + 2t - st < 0$. As expected, when $k_1 = k_2 = h$ (i.e., there is no imprinting), the polymorphic equilibrium allele frequencies for the incomplete inactivation model (6) are equivalent to (9).

Interestingly, it is not possible to recover the polymorphic equilibrium for the incomplete imprinting model (6) by substituting $h = 0.5(k_1 + k_2)$ into (9). In general, ignoring imprinting (i.e., setting $h = 0.5(k_1 + k_2)$) underestimates the frequency of A_1 when $k_1 < k_2$ and overestimates the frequency of A_1 when $k_2 < k_1$. For an autosomal imprinted locus, the expected response to selection in one generation is equivalent whether calculated using separate terms for the reciprocal heterozygotes or simply using the heterozygote mean value (Santure and Spencer 2011). The lack of

equivalence in the X chromosome system is likely due to the lack of symmetry in the interaction between the male and female allele frequencies (and hence the male selection parameter t) and the k_i imprinting parameters in the allele frequency recursions (5).

Tables 4 and 5 compare mutation-selection balance at an X-linked locus for mutation rates μ (from A_2 to A_1 , when A_2 would be fixed by selection alone) and ν (from A_1 to A_2 , when A_1 would be fixed by selection alone), respectively. Despite the lack of equivalence of the polymorphic equilibrium when substituting $h = 0.5(k_1 + k_2)$ into (9), both Table 4 and Table 5 show an interesting correspondence between the equilibrium frequencies with and without imprinting. For both mutation rates (ignoring terms in μ^2 and ν^2 and above), the feasibility condition for mutation-selection balance with no imprinting and $h = 0.5$ is both the sum of the feasibility conditions under paternal and maternal imprinting, and the sum of the feasibility conditions with no imprinting and $h = 0$ and $h = 1$. The feasibility conditions are also in general the denominators of each equilibrium. From comparison with the no imprinting, $h = 1/2$ case for both mutation rates, it is clear that the frequency of the deleterious allele is at similar frequency to that at imprinted loci when similar selection pressures apply. The rightmost column in each table gives a numerical example.

There is an extensive literature regarding the existence and maintenance of variability on the X chromosome. In the context of sexual conflict and over a range of dominance, the X chromosome has less opportunity for polymorphism than the autosomes (Curtsinger 1980; Patten and Haig 2009). However, the speed to fixation of beneficial X-linked compared to autosomal alleles is dependent not only on the degree of dominance, but also factors including the

Table 5 Comparison of mutation-selection balance with and without imprinting at a sex-linked locus for mutation rate ν from A_1 to A_2 , ($s, t \leq 1$, $\nu > 0$)

	$\hat{p}_f$ (females)	$\hat{p}_m$ (males)	Feasibility condition	$(1 - \hat{p}_f, 1 - \hat{p}_m)$ for $s = -0.1$, $t = -0.2$, $\nu = 10^{-5}$
Complete paternal X inactivation	$1 - \nu \left[\frac{3(s-1)(t-1)}{2st-s-t} \right]$	$1 - \nu \left[\frac{2st-4s-t+3}{2st-s-t} \right]$	$2st-s-t > 0$	$(11.6 \times 10^{-5}, 10.7 \times 10^{-5})$
Complete maternal X inactivation, female offspring only	$1 - \nu \left[\frac{(2s-3)(t-1)}{st-s-t} \right]$	$1 - \nu \left[\frac{(s-1)(t-3)}{st-s-t} \right]$	$st-s-t > 0$	$(12.0 \times 10^{-5}, 11.0 \times 10^{-5})$
Complete maternal X inactivation, male and female offspring	$1 - \nu \left[\frac{2s-3}{s} \right]$	$1 - \nu \left[\frac{3(s-1)}{s} \right]$	$s < 0$	$(32.0 \times 10^{-5}, 33.0 \times 10^{-5})$
No imprinting; $h = 0^a$	$1 - \nu \left[\frac{(2s-3)(t-1)}{2st-2s-t} \right]$	$1 - \nu \left[\frac{2st-4s-t+3}{2st-2s-t} \right]$	$2st-2s-t > 0$	$(8.7 \times 10^{-5}, 8.3 \times 10^{-5})$
No imprinting and no dominance; $h = 0.5^a$	$1 - \nu \left[\frac{5st-5s-6t+6}{3st-2s-2t} - \frac{3st-2s-2t}{2st} \right]$	$1 - \nu \left[\frac{3st-7s-2t+6}{3st-2s-2t} \right]$	$3st-2s-2t > 0$	$(11.8 \times 10^{-5}, 10.8 \times 10^{-5})$
No imprinting; $h = 1^a$	$1 - \nu \left[\frac{3(s-1)(t-1)}{st-t} \right]$	$1 - \nu \left[\frac{(s-1)(t-3)}{st-t} \right]$	$st-t > 0$	$(18.0 \times 10^{-5}, 16.0 \times 10^{-5})$

^a Where $(1 - hs)$ is the viability of the heterozygous females; see Table 1.

population-effective population size, the effective population size of the X compared to the autosomes, the reproductive variability of males compared to females, and the relevance of standing vs. new mutations (Rice 1984; Charlesworth *et al.* 1987; Vicoso and Charlesworth 2006; Mank *et al.* 2009; Connallon and Clark 2010; Connallon *et al.* 2012), suggesting that these factors are also likely to influence polymorphism on the X chromosome. In addition, the X chromosome is predicted to harbor a large proportion of sexually antagonistic loci (Gibson *et al.* 2002, although see Connallon and Clark 2010). We have demonstrated that unless there is strong yet balanced sexual conflict, imprinting (either complete or incomplete) is unlikely to be conducive to selectively maintained polymorphism on the X chromosome.

In summary, imprinting of X-linked genes means that the conditions for the selective maintenance of allelic variation are either nonexistent (for complete maternal inactivation) or restrictive, requiring male and female selection coefficients of opposite sign but similar magnitude (for complete paternal inactivation and when imprinting is incomplete). Our results therefore add to the reasons for expecting less variation on this chromosome. Finally, we have shown that the frequency of an allele maintained by mutation–selection balance on the X chromosome is very similar for both a locus without imprinting and an imprinted locus.

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GENETICS

Supporting Information

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Genomic Imprinting Leads to Less Selectively Maintained Polymorphism on X Chromosomes

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Files S1-S3

Supporting Files

File S1 A Wolfram Mathematica 8 (Wolfram Research, Inc.) file with the mathematical derivations for selection and selection-mutation models of X-linked complete paternal and maternal inactivation, and incomplete inactivation, of a single locus with two alleles

File S2 A Wolfram Mathematica 8 (Wolfram Research, Inc.) file with the mathematical derivations for selection and selection-mutation models of autosomal paternal and maternal inactivation of a single locus with two alleles

File S3 A Wolfram Mathematica 8 (Wolfram Research, Inc.) file with the mathematical derivations for selection and selection-mutation models of dominance for a single X-linked locus with two alleles

SUPPORTING INFORMATION REFERENCE

Wolfram Research, Inc., Mathematica, Version 8.0, Champaign, IL (2011).