Studies on Metatherian Sex Chromosomes II*. The Improbability of a Stable Balanced Polymorphism at an X-linked Locus with the Paternal X Inactivation System of Kangaroos

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Abstract

Female kangaroos and perhaps other female marsupials have a unique form of dosage compensation for X-linked genes in their soma. In these animals the paternal X is inactive. Heterozygote females therefore have the phenotype of one or the other of the homozygotes, with the allele which is expressed coming from their mother. The unexpressed paternally derived allele may, however, be transmitted to the next generation in the usual Mendelian manner and there be expressed. Such a combination of haploid phenotypic expression and diploid genotypic behaviour on the part of X-linked genes in kangaroos makes their population genetics unique. This paper examines the possibilities for balancing selection in the kangaroo X chromosome system and shows that balanced polymorphisms are unlikely to occur. If $1-a$, 1, $1-b$ and 1 are the selection coefficients of the α_1 females, α_2 females, α_1 males and α_2 males respectively (where α_1 is the phenotype when A_1 is expressed and α_2 the phenotype when A_2 is expressed), then the equilibrium is reached when the gene frequency of A_1 in females $= 0 \cdot 5(a^{-1}+b^{-1})$, which takes values between 0 and 1 for only a few of the biologically likely values of a and b.

Introduction

Although kangaroos have the same chromosomal system of sex determination as eutherian mammals (Sharman *et al.* 1970) they have a different system of dosage compensation in which the paternally derived X in the soma of females is inactive (reviewed in Sharman 1973; Cooper *et al.* 1975*a*, 1975*b*). The chromosome which is inactive may nonetheless be transmitted to the next generation and then be expressed in a normal manner. This behaviour makes the population genetics of X-linked genes in kangaroos unique. Consider an X-linked locus with two alleles, denoted A_1 and A_2. The homozygotes A_1A_1 and A_2A_2 have the phenotypes α_1 and α_2 respectively, whilst the heterozygotes are of two kinds, denoted A_1A_2 and A_2A_1. In A_1A_2 the allele A_1 is derived from the mother and the phenotype is α_1, whilst in A_2A_1 the A_2 allele is from the mother and the phenotype is α_2. Thus female kangaroos have haploid expression for their X chromosomes but genotypically they behave as a diploid, with heterozygotes showing segregation and transmission of alleles in Mendelian manner, as has been demonstrated in the first paper in this series (Johnston and Sharman 1975). It is the purpose of this paper to give the conditions for stable balanced polymorphism at a sex-linked locus with paternal X inactivation. It will be shown that stable balanced polymorphism is in principle possible but that the conditions which must obtain are so restrictive as to render it unlikely in nature.

Polymorphic Equilibrium with Fixed Selection Coefficients for Each Phenotype in the Two Sexes

Let P_f and $1-P_f$ be the frequencies of the alleles A_1 and A_2 respectively in the gametes produced by the females of the nth generation after selection has acted upon these females. Let P_m and $1-P_m$ be the corresponding male frequencies. The expected genotypic and phenotypic frequencies in the $(n+1)$th generation zygotes before selection are then as in Table 1. The α_1 phenotype has a selection coefficient

Table 1. Frequencies and selection coefficients for the genotypes and phenotypes at a two-allele sex-linked locus whose mode of dosage compensation is paternal X inactivation

	Females[A]				Males	
Genotypes	A_1A_1	A_1A_2	A_2A_1	A_2A_2	A_1	A_2
Genotypic frequencies	P_fP_m	$P_f(1-P_m)$	$(1-P_f)P_m$	$(1-P_f)(1-P_m)$	P_f	$1-P_f$
Phenotypes	α_1		α_2		α_1	α_2
Phenotypic frequencies	P_f		$1-P_f$		P_f	$1-P_f$
Selection coefficients	$1-a$		1		$1-b$	1

[A] Note that A_1A_2 is distinguished from A_2A_1 with the allele contributed by mother being written first. P_f and $1-P_f$ are the frequencies of A_1 and A_2 in the gametes of the nth generation of females after selection; P_m and $1-P_m$ are the corresponding male frequencies in the nth generation.

of $1-a$ in females and $1-b$ in males and the α_2 phenotype has selection coefficients of 1 in both sexes. The values a and b are assumed to be constant. The gene frequencies for A_1 in the gametes produced by the two sexes of the $(n+1)$th generation after selection has acted upon the $(n+1)$th generation zygotes are as follows, where the prime signifies the frequencies in the $(n+1)$th generation:

$$P_f' = \frac{2(1-a)P_fP_m + (1-a)P_f(1-P_m) + (1-P_f)P_m}{2[(1-a)P_f + 1 - P_f]}$$

$$= 0\cdot5[1 + P_m - (1-P_f)/(1-aP_f)], \tag{1}$$

$$P_m' = (1-b)P_f/(1-bP_f)$$

$$= 1 - (1-P_f)/(1-bP_f). \tag{2}$$

At equilibrium $P_f' = P_f$ and $P_m' = P_m$. When these conditions are imposed upon equations (1) and (2) a cubic results:

$$P_f(1-P_f)(a+b-2abP_f) = 0. \tag{3}$$

The equilibrium frequencies in the females are therefore

$$\hat{P}_f = 0, \quad 1, \quad \text{and} \quad 0\cdot5(a^{-1}+b^{-1}),$$

and in males

$$\hat{P}_m = 0, \quad 1, \quad \text{and} \quad (1-b)(a+b)b^{-1}(a-b)^{-1}.$$

The non-trivial equilibrium frequency for females is symmetrical in a and b and is the inverse of their harmonic mean. In the Appendix it is shown that this equilibrium is stable for all $0 < \hat{P}_f < 1$.

As is to be expected, $\hat{P}_f$ does not lie between 0 and 1 when a and b are both positive and less than one, i.e. when A_1 is being selected against in both sexes. Nor does $\hat{P}_f$ lie between 0 and 1 when a and b are both negative, i.e. when A_1 is being selected for in both sexes. An equilibrium with biological meaning will exist provided that $0 < a^{-1} + b^{-1} < 2$, which is true for some values of a and b when a and b have opposite signs. Without loss of generality we can let $0 < a < 1$. Then it follows that $b < 0$ and $|b| > a$ to satisfy $a^{-1} + b^{-1} > 0$. Some values of a and the corresponding range of values for b for which $0 < a^{-1} + b^{-1} < 2$ are given in Table 2. This Table

Table 2. Some examples of combinations of the selection coefficients in the two sexes which lead to equilibrium at a sex-linked locus with paternal X inactivation

The values of a have been chosen arbitrarily and the corresponding values of b calculated. But since the equilibrium frequency is symmetrical in a and b, the two parameters can be interchanged. α_1 = phenotype of A_1A_1 and A_1A_2 and α_2 = phenotype of A_2A_1 and A_2A_2, where the allele written first in the heterozygote is from the mother. See Table 1 and text for the other conditions of selection

a	Limits of b		Selection coefficient of α_1 in females[A]	Limits of possible selection coefficients of α_1 in males[A]
	Upper	Lower		
0·01	−0·01	−0·01020	0·99	1·01–1·0102
0·02	−0·02	−0·02083	0·98	1·02–1·02083
0·05	−0·05	−0·055˙	0·95	1·05–1·055˙
0·10	−0·10	−0·125	0·90	1·10–1·125
0·20	−0·20	−0·333˙	0·80	1·20–1·33˙
0·30	−0·30	−0·75	0·70	1·30–1·75
0·40	−0·40	−2	0·60	1·40–3
0·45	−0·45	−4·5	0·55	1·45–5·5
0·50	−0·50	None, $b \rightarrow -\infty$	0·50	1·50

[A] Where α_2 has a coefficient of 1.

shows that for weak selection an equilibrium is very unlikely since the values of a and b must fall within very narrow limits if $\hat{P}_f$ is to be between 0 and 1. It is only with strong selection that there is a wider range of values which b can take for a given a. For example if the ratio of selection coefficients of α_1 to α_2 in the females is $0·99 : 1$ then the equilibrium is possible if the ratio in the males is $1·0100 : 1·0102$. But if the ratio is $0·60 : 1$ in females, the ratio can lie between $1·4 : 1$ and $3·0 : 1$ in males.

A gene which is highly deleterious or lethal in one sex can be maintained if there is sufficiently strong selection in its favour in the other sex. As b approaches $-\infty$, i.e. as α_2 tends towards a lethal phenotype in males, $\hat{P}_f$ approaches $0·5a^{-1}$, so that $\hat{P}_f < 1$ if $0·5 < a < 1$. This means that genotypes lethal in one sex can be maintained if selection is at least $2 : 1$ in their favour in the other sex, a biologically unlikely set of circumstances.

It is interesting to examine the case where the α_1 phenotype (say) is selected for in one sex and selected against with equal intensity in the other, i.e. where $1 : 1 - a = 1 - b : 1$. To do so it is convenient to change the notation for our selection coefficients. Let α_1 and α_2 in females have the selection coefficients $1 - u$ and 1 and in the males 1

and $1-v$, i.e. $a = u$ and $b = v/(v-1)$. The non-trivial equilibrium becomes $\hat{P}_f = 0.5(1 + u^{-1} - v^{-1})$, i.e. if $u = v$, which corresponds to selection of equal but opposite intensity in the two sexes, then $\hat{P}_f = 0.5$.

Given a fixed selection coefficient for each phenotype it is impossible for the heterozygote at an X-linked locus in kangaroos to be superior to both homozygotes. But although heterozygotes usually cannot be identified phenotypically (see below for the exceptions to this), they can be identified genotypically if they give rise to progeny with the opposite phenotype to their own. If selection were to be based upon an interaction between parent and offspring, for example between mother and intra-uterine or intra-pouch young, then heterozygote superiority might be possible. It seems plausible that this would happen if the offspring were at an advantage if carried by a mother with a phenotype unlike her own. A rigorous demonstration that this is so has not been carried out. Whether it would be of any value to do so depends upon how likely such interactions are. It is difficult to comment on this possibility in the present state of knowledge, but one suspects that such interactions could only operate with respect to a very small fraction of loci on the X chromosome.

Discussion

It seems clear that with complete paternal X inactivation as the system of dosage compensation, balanced polymorphism is most unlikely. It should, however, be noted that the assumption of complete paternal X inactivation may not be true for all kangaroo sex-linked loci. Two sex-linked polymorphisms have been well described in kangaroos. For the glucose-6-phosphate dehydrogenase (G6PD) locus no evidence for the expression of the paternal allele in heterozygotes has been found other than in cells grown in culture (Cooper *et al.* 1975*b*; Johnston and Sharman 1975). But for the phosphoglycerate kinase A (PGK-*A*) locus two kinds of tissues exist (VandeBerg *et al.* 1973). One of these is represented by the blood and has only the maternal allele expressed. The other, represented chiefly by muscle tissue, has full expression of the maternal allele and weak expression of the paternal allele. Heterozygotes are accordingly distinguishable but they differ from ordinary heterozygotes in having unequal expression of the two genes. There is therefore some chance that PGK-*A* heterozygotes could have a selection coefficient different from that of the homozygotes. But physiologically it seems more likely that even PGK-*A* heterozygotes closely resemble one or the other of the two homozygotes. On this preliminary evidence complete paternal X inactivation seems to represent a reasonable assumption upon which to base an investigation of the effect of selection on sex-linked genes in kangaroos.

The conditions which must be satisfied if there is to be a stable balanced polymorphism at an X-linked locus in eutherian mammals or at any locus in a haplodiploid organism were first given in a general form by Bennett (1957, 1958) and have been confirmed by several other authors (Mandel 1959; Haldane and Jayakar 1964; Cannings 1967). In essence the conditions for equilibrium are of two kinds. One kind involves heterozygote superiority in females, provided that the selection coefficients in males are restricted to a certain range. The other kind involves selection in opposite directions in the two sexes without superiority of the heterozygote, with some restriction upon the relative values which selection coefficients may take between the sexes.

By contrast with ordinary sex linkage the paternal X inactivation system does not allow heterozygote superiority if the possibility of interactions between mother

and offspring are ignored. Moreover in the paternal X inactivation system the conditions for equilibrium through selection in the opposite direction in the two sexes are more restrictive than in ordinary sex linkage. This can be seen most clearly for weak selection with gene frequencies almost equal in the two sexes. Under these conditions the paternal X inactivation system is very nearly a special case of ordinary sex linkage in which the heterozygote is constrained to have a selection coefficient which is the mean of those for the two homozygotes. If one places this constraint upon the conditions given by Bennett (1957, 1958) or Haldane and Jayakar (1964) the same conclusion as in this paper is reached, namely that equilibrium is possible but not likely.

Acknowledgments

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Appendix

Conditions for Stability of the Equilibrium

The conditions for stability may be obtained by the method used by Haldane and Jayakar (1964). Let $P_f = \hat{P}_f + x_n$, and $P_m = \hat{P}_m + y_n$, then for small x_n and y_n it is approximately true that

$$x_n = A_1\lambda_1^n + A_2\lambda_2^n,$$

$$y_n = B_1\lambda_1^n + B_2\lambda_2^n,$$

where λ_1 and λ_2 are the roots of the determinant

$$\begin{vmatrix} \partial P_f'/\partial P_f - \lambda & \partial P_f'/\partial P_m \\ \partial P_m'/\partial P_f & \partial P_m'/\partial P_m - \lambda \end{vmatrix} = 0.$$

We have from equations (1) and (2) of the text

$$\partial P_f'/\partial P_f = 0 \cdot 5(1-a)(1-aP_f)^{-2}$$

$$\partial P_m'/\partial P_f = (1-b)(1-bP_f)^{-2}$$

$$\partial P_f'/\partial P_m = \tfrac{1}{2}$$

$$\partial P_m'/\partial P_m = 0$$

so that

$$\lambda^2 - \lambda(\partial P_f'/\partial P_f) - (\partial P_f'/\partial P_m)(\partial P_m'/\partial P_f) = 0.$$

The values of the coefficients in the above quadratic are given by values of $\hat{P}_f$. P_f will tend to $\hat{P}_f$ and P_m to $\hat{P}_m$ if λ_1 and λ_2 are both between ± 1. The quadratic $\lambda^2 - A\lambda - B$ will have roots between ± 1 if $A + B < 1$ where A and B are both positive. For $\hat{P}_f = 0 \cdot 5(a^{-1} + b^{-1})$ this means

$$2(a-b)^{-2}[b^2(1-a) + a^2(1-b)] < 1.$$

Multiplying by $(a-b)^2 2^{-1} a^{-2} b^{-2}$ we obtain

$$0 \cdot 5a^{-2} + 0 \cdot 5b^{-2} + a^{-1}b^{-1} < a^{-1} + b^{-1}$$

which is equivalent to $\hat{P}_f^2 - \hat{P}_f < 0$ which is true if $0 < \hat{P}_f < 1$, so that the equilibrium $\hat{P}_f = 0 \cdot 5(a^{-1} + b^{-1})$ is stable for all $0 < \hat{P}_f < 1$. It should also be noted that it can be easily shown that $0 < \hat{P}_m < 1$ whenever $0 < \hat{P}_f < 1$.