Testing the unguarded X hypothesis

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1 Introduction

The unguarded X (UX) hypothesis states that one reason for females to live longer than males is that they are usually the homogametic sex. This implies that either somatic or inherited (partially) recessive deleterious mutations in the X chromosome are always exposed in males, but concealed in heterozygous females. This hypothesis requires recessive mutations, maintained by mutation-selection balance, that negatively affect longevity both in males and in females. This scenario is hardly controversial. The main uncertainty is whether this kind of mutations can fully explain the difference in longevity between sexes.

The alternative hypothesis is that a different kind of mutations is required to account for the difference in longevity between males and females. Namely, sexually antagonistic mutations, which are maintained at relatively high frequencies in the population by a selection balance. Sexually antagonistic mutations could happen in any chromosome. However, there are theoretical reasons and evidence to belive that they are especially frequent in the X chromosome [Gibson et al., 2002].

Kelly [1999] suggested an experiment to determine if low-frequency, deleterious mutations can explain the observed genetic variance in a character that is correlated with fitness. The alternative is that high-frequency mutations maintained by a selection balance are required to explain the observed variance. The experiment is relatively easy and it involves a short selection experiment and two short inbreeding experiments. If most genetic variance in the character is due to a mutation-selection balance, the response to selection, small as it may be, will be comparable to the effect of inbreeding. However, in the case of any selection balance (antagonistic pleiotropy or overdominance), the response to selection is expected to be very low, while the effect of inbreeding relatively high. Needless to say that the conclusion would only apply to the population used in the experiment.

Kelly probably did not have in mind a sex-specific character when he suggested such an experiment. And he did not attempt to guess on what chromosome the relevant variants were located. Thus, we need to make sure if the UX hypothesis can be tested

with a similar experiment, and exactly how it should be performed. The right thing to do would be to derive the expectations of the relevant quantities (covariance of additive effects and homozygous dominance effects, C_{ad}, and additive variance, V_a) of a dimorphic character taking into account that at least some loci must be in the X chromosome. This may have been done, but I have not found it yet in the literature.

Before getting there, I want to note that Charlesworth and Hughes [1996] assume frequencies of mutant alleles are low, even though they may affect survival only late in life. This is also an assumption we need to justify the application of Kelly's method to test the UX hypothesis. It could be questioned, because a low selection coefficient against such mutations suggests they could behave as (almost) neutral and eventually drift to not-so-low frequencies.

2 Genetic variance components

Charlesworth and Hughes [1996] cite Falconer [1989] and Mukai et al. [1974] as sources of the standard formula for additive genetic variance. In chapter 7, Falconer [1989] assigns genotypic values $-a$, d, and a to genotypes A_2A_2, A_1A_2, and A_1A_1, respectively. If the frequency of allele A_1 is p and that of A_2 is q, and assuming Hardy-Weinberg, the average genotypic value at one locus is $a(p-q)+2dpq$ [Falconer, 1989, p. 114].

Mukai et al. [1974] considers a locus affecting fitness, and therefore uses a different parameterization. The genotypic values (fitness) corresponding to genotypes A_2A_2, A_1A_2, and A_1A_1 (again in increasing order) are now $1-s$, $1-hs$, and 1, respectively. In this case, assuming Hardy-Weinberg equilibrium, the average genotypic value is $1-2pqhs-q^2s$. Note that in this case we could also assume that the population is at mutation-selection equilibrium. Then, according to classic theory, the frequency of A_2 should be something like μ/hs.

The total genetic variance due to one locus with two alleles can be easily derived for a population in Hardy-Weinberg equilibrium by finding the expected squared deviation from the mean of the genotypic values. Total genetic variance at one locus can be decomposed in additive, V_A, and dominance, V_D, components. Table 1 shows de expressions of genetic variance components found in both sources. Falconer [1989, p. 135] gives detais of how to derive those expressions.

So far, the locus is assumed to be autosomal. What would the genetic variance of an X-linked locus be?

3 Genetic variance of an X-linked locus

I assume for simplicity that sex-ratio is balanced, and that the heterogametic (male) genotypes have the same genotypic values as the corresponding homozygotes (see Ta-

Table 1: Genetic variance components at one autosomal locus, expressed according to either Falconer [1989] or Mukai et al. [1974].

Component	Falconer	Mukai et al.
Additive	$2pq[a+d(q-p)]^2$	$2pqs^2[(p-q)h+q]^2$
Dominance	$(2pqd)^2$	$p^2q^2s^2(1-2h)^2$
Total	$2pq[a+d(q-p)]^2+[2pqd]^2$	$pqs^2[2(1-2pq)h^2-4q^2h+q(1+q)]$

Table 2: Genotype values in one X-linked locus with two alleles. The mean genotype value is $a(p-q)+pqd$.

	A_1A_1	A_1A_2	A_2A_2	A_10	A_20
Frequency	$\frac{1}{2}q^2$	pq	$\frac{1}{2}q^2$	$\frac{1}{2}p$	$\frac{1}{2}q$
Gen. value	a	d	$-a$	a	$-a$
Deviance	$q(2a-pd)$	$a(q-p)+d(1-pq)$	$-p(2a+qd)$	$q(2a-pd)$	$-p(2a+qd)$
Breed. val.	$q(3a+d(q-p))$	$\frac{3}{2}a(q-p)+d(\frac{1}{2}-2pq)$	$-p(3a+d(q-p)$	$q(a+d(q-p))$	$-p(a-d(q-p))$
Breed. val. (α)	$2q\alpha$	$\alpha(q-p)$	$-2p\alpha$	$\frac{2}{3}q(\alpha+d(q-p))$	$-\frac{2}{3}p(\alpha-2d(q-p)$

ble 2). The average genotypic value of an X-linked gene is $a(p-q)+pqd$, which is slightly different from the mean genotypic value of an autosomal locus ($a(p-q)+2pqd$). The average gene effects also change. If my calculations are correct, the average effect of allele A_1 is $\alpha_1 = q(\frac{3}{2}a+d(\frac{1}{2}-p))$, and that of allele A_2 is $\alpha_2 = -p(\frac{3}{2}a+d(q-\frac{1}{2}))$. The average effect of substituting an A_2 allele for an A_1 is $\alpha = \frac{3}{2}a+\frac{1}{2}d(q-p)$. Note that the following relationships hold for both autosomal and X-linked genes: $\alpha = \alpha_1 - \alpha_2$; $\alpha_1 = q\alpha$; and $\alpha_2 = -p\alpha$. Perhaps a third, null allele should be considered in the Y chromosome, although it cannot be substituted. In any case, it's average effect would be $-pqd$.

The breeding value of a genotype is twice the expected genotypic value of its progeny, expressed usually as deviation from the population average. Note that for male genotypes, the breeding values do not coincide with the sum of the average effects of their alleles. Thus, their expressions in terms of α are not simpe.

I did find some references about the genetic variance in sex-linked loci James [1973], Cowley et al. [1986], Connallon and Knowles [2006]. Formulas depend on the model details and the parameterization of effects. But my intuition that two subpopulations need to be treated separately (males and females) is confirmed. There seems to be much classic theory to extrapolate to the case of X-linked loci. I have not found sex-linked loci mentioned in Falconer [1989]. But I need to focus on the application of Kelly [1999] to

X-linked loci.

4 The experiment

In Kelly's terms, M is the mean phenotype in the population. The directional dominance, B, is the difference in mean phenotype between an outbred population and a completely inbred population with the same allele frequencies. V_a is the additive genetic variance, and V_p, the total phenotypic variance. C_{ad} is the covariance between the additive effects and the homozygous dominant effects. "The 'homozygous dominant effect' is the dominance deviation associated with a particular allele when that allele is in homozygous form.'

Citing Kelly [1999], who refers to a character (mostly) affected by autosomal loci: "In the short term, the expected change in the mean phenotype (M) equals the product of the cumulative selection differential and the narrow sense heritability [Falconer, 1989]. The latter is V_a divided by V_p, the phenotypic variance. The expected change in the directional dominance (B) is the product of the cumulative selection differential and C_{ad}/V_p [...]. Thus, the ratio of the cumulative change in B to the cumulative change in M provides an estimate of the ratio of C_{ad} to V_a." And the estimate of C_{ad}/V_a is known to be sensitive to the frequency of partially recessive alleles.

A sex-linked trait has different genetic variances in males and females. If the trait is defined as sex-specific, and therefore selected only in one sex, the expected change in mean (sex-specific) phenotype would still be the product of the cumulative selection differential and the narrow sense (sex-specific) heritability (I think, because this expectation stems only from the definition of heritability [Falconer, 1989, page XX]). This may be the only way to target female longevity, irrespectively of its correlation with male longevity. However, in a population of flies, it is unfeasible to manually select individuals according to the longevity of their mother. Even if individual flies could be marked with their mother's code, marking and reading the codes would not be easier than having the population separated in sex- and family-specific bottles, which is undesirable. A more efficient solution is required. Actually, the literature suggests some options.

Lund-Hansen [2017, p. 19] claims to be the first case of sex-limited evolution in *Drosophila* that targets females, instead of males. Furthermore, she limits evolution to the X chromosome. That's exactly what we need. Her purpose is just to eliminate male selection on the X chromosome. The female-limited X-chromosome evolution experiment releases sexually antagonistic standing genetic variation from the selection balance, and allows the fixation of alleles beneficial to females in the X chromosome. She accomplishes this by using an X-chromosome balancer and a smart design of crosses. For details, see chapter 2 of Lund-Hansen [2017], which is available online here. First, she introgresses an X-chromosome balancer (FM) into the source population (12 generations of back-crossing). The introgressed population provides a source of males with an FM

X-chromosome (FM/Y). In her experiment, a population is a set of 14 vials, with 16 males and 16 females each. In the experimental evolution group, females in a vial are heterzygous FM/X, and the males are FM/Y, so that all the daughters inherit an evolving X chromosome from their mother and an FM balancer from their father. Females must be collected as virgins every generation. In order to allow recombination among evolving X chromosomes, every generation a subset of 16 FM/X females where mated not with FM/Y males, but with X/Y males from the same population. The two evolving X chromosomes in any of their daughters would recombine. When mated with FM/Y males, they would produce FM/X daughters that would go back to the selective regime, one to each of the 14 vials. On the side, Lund-Hansen raised two types of control populations. Each of the three types of populations was replicated four times. That makes $3 \times 4 \times 14 = 168$ vials. The experiment went on over 40 generations.

For our purpose, in the populations undergoing female-limited X-chromosome evolution we would have to select for longevity. I think that 20 generations should be enough.

To summarize, we would need to: 1) run an inbreeding experiment from the source population to estimate B before the selection experiment; 2) measure the average female longevity in the source population; 3) run a female-limited X-chromosome evolution experiment selecting for female longevity; 4) measure the average female longevity after the selection experiment; and 5) run a second inbreeding experiment from the evolved population. Actually, the 'inbreeding experiments' whould be as short as two or three generations, because they need to affect only the X chromosome. An FM/X female, carrying the X chromosme targeted from homozygosity, would be crossed with an unrelated FM/Y male. Among the progeny, an X/Y male would be crossed with an FM/X sister. The X/X progeny would be homozygous for the whole X chromosome. However, the parents being siblings, the other chromosomes would also be partially inbred. To minimize the contribution from autosomes, half-siblings could be used.

5 Apendix

References

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