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 intermediate 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. It is a qualitative test, rather than a quantitative measure of the contribution of each frequency class. The experiment is relatively easy and it involves a short selection experiment and two short inbreeding experiments. Needless to say that the conclusion would only apply to the population used in the experiment.

The method is based on a simple model. In every locus (assumed to be autosomic) affecting a trait correlated with fitness, there are a high allele (A_{1i}), and a low allele (A_{0i}). The three genotypes in one locus, from low to high, have genotypic values $-a_i$, d_i, and a_i, where $-a_i \leqslant d_i \leqslant a_i$. The frequency of A_{1i} is p_i, and that of A_{0i}, q_i. For simplicity, I drop the i subscript. Under this parameterization, the additive genetic variance contributed

by one locus in a population in Hardy-Weinberg equilibrium is $V_a = 2pq[a + d(q - p)]^2$ Falconer [1989, p. 126].

The other magnitude of interest is the covariance of additive effects with the homozygous dominance effects, C_{ad}. The additive effects are what Falconer [1989, p. 112] calls average effects, say a_j and a_k of alleles j and k. The breeding value of an autosomal genotype can be expressed as the sum of the average effects of the two alleles [Falconer, 1989, p.115]. And the difference between the breeding value and the genotypic value is the dominance deviation, say d^j_k for genotype jk. The homozygous dominance effect of allele j is d^j_j, the difference between genotypic and breeding values of genotype jj, due to dominance. Thus, the covariance between average effects and homozygous dominance effects, C_ad is highest when low alleles (A_0) are recessive and high alleles (A_1), dominant. Cockerham and Weir [1984] defines this covariance for one locus, i, as $d_{1i} = \sum_j p_{ji} a_{ji} d^j_{ji}$. This stems from the definition of covariance ($\mathrm{Cov}[a, d] = \mathrm{E}[ad] - \mathrm{E}[a]\mathrm{E}[d]$), and from the fact that the expected average effect among the alleles in one locus ($\mathrm{E}[a]$) is zero. If there are two alleles in the locus, p_{ji} in that formula are p and $q = 1 - p$. If q is the frequency of the low allele, A_0, then $a_{0i} = -p(a+d(q-p))$, and $a_{1i} = q(a+d(q-p))$. The homozygous dominant effects in this model are $d^0_{0i} = -2p^2d$, and $d^1_{1i} = -2q^2d$ [Falconer, 1989, p. 118]. Substituting these values in the formula above, we obtain the expression for C_{ad} given by Kelly [1999]: $C_{ad} = 2pq(p - q)d[a + d(q - p)]$.

When several loci are involved, the additive variance is the sum of V_a across loci [Falconer, 1989, p. 129], and the covariance between average effects and homozygous dominance effects, C_{ad}, is also the sum of the covariances across all loci [Cockerham and Weir, 1984]. In principle, there are ways to estimate and C_{ad} and V_a. These quantities are interesting because their ratio, C_{ad}/V_a, is sensitive to the allele frequencies. When the low alleles have intermediate frequencies, C_{ad}/V_a drops to values close to or lower than zero. Kelly [1999] proposes a new and efficient way to estimate directly the ratio C_{ad}/V_a. A positive value would indicate that low alleles are at low frequencies.

2 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.' Note that Cockerham and Weir [1984] uses the symbol d_{1i} for what Kelly calls C_{ad}.

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 evolu-

tion 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.

3 Apendix

References

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