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SHORT COMMUNICATION

Estimating the heritability of female lifetime fecundity in a locally adapted *Drosophila melanogaster* population

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Abstract

The heritability of genome-wide fitness that is expected in finite populations is poorly understood, both theoretically and empirically, despite its relevance to many fundamental concepts in evolutionary biology. In this study, we used two independent methods of estimating the heritability of lifetime female fecundity (the predominant female fitness component in this population) in a large, outbred population of *Drosophila melanogaster* that had adapted to the laboratory environment for over 400 generations. Despite strong directional selection on adult female fecundity, we uncovered high heritability for this trait that cannot be explained by antagonistic pleiotropy with juvenile fitness. The evolutionary significance of this high heritability of lifetime fecundity is discussed.

Introduction

The heritability of fitness is a key parameter for many fundamental questions in evolutionary biology including the adaptive significance of sexual recombination (Williams, 1975; Maynard Smith, 1978) and the process of sexual selection (Andersson, 1994). At a single locus, and with feasible mutation rates, Fisher's (1930) fundamental theorem of natural selection predicts low heritability of fitness at equilibrium. However, genome-wide models with the same per-locus mutation rates predict substantial heritability for fitness (Lande, 1975; Kondrashov, 1988; Rice, 1988; Charlesworth, 1990), as do recent models for the standing genetic variation for arbitrary quantitative traits (Zhang *et al.*, 2004; Zhang & Hill, 2005).

Empirical studies estimating the heritability for net fitness have produced variable outcomes. Several long-term multigenerational field studies (such those on red deer by Kruuk *et al.*, 2000; collared flycatchers by Merilä & Sheldon, 2000; and great tits by McCleery *et al.*, 2004) have estimated heritability of net fitness to be small and frequently at or near zero. This was not due to an absence of additive genetic variation for fitness (measured as the additive coefficient of variation for net fitness, CV_A; see Houle, 1992), which was in most cases large for both males and females, but instead was due to high environmental/nonadditive genetic variances for traits closely related to fitness. Not all studies, however, have yielded such low estimates of fitness heritability. A recent study of preindustrial humans (Pettay *et al.*, 2005), found that female (but not male) fitness exhibited significant heritability ($h^2 = 0.47$), despite high levels of nonadditive variation for fitness. Estimates of standing genetic variance for fitness and its heritability have also been observed to be high for laboratory populations of *Drosophila melanogaster*. Fowler *et al.* (1997) and Gardner *et al.* (2005) used a multigeneration assay utilizing balancer chromosomes (which suppress recombination) to estimate the variance in net fitness for a small sample of chromosomes III. They found substantial heritable net fitness variation, although much of this was due to a small number of chromosomes with extreme fitness values. Hemiclonal techniques (described in Chippindale *et al.*, 2001) that cause nearly genome-wide groups of genes to co-segregate like a single, nonrecombining chromosome also suggest that there is a considerable amount of heritable genome-wide variation for net fitness for both the sexes (Chippindale *et al.*, 2001; Pischedda & Chippindale, 2006).

In this study, we set out to estimate the heritability of adult female fitness (lifetime female fecundity) in a large, outbred *D. melanogaster* population that had adapted to a laboratory environment for over 400 generations. In this first study, we measured fitness in females, with measures of heritability of male fitness planned for a future

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study. Here, we focus on adult fitness because a previous study with our laboratory population indicated that nearly all fitness variation occurs in the adult rather than in the juvenile stages and because there is no measurable correlation between juvenile and adult fitness among nearly genome-wide hemiclones (Chippindale *et al.*, 2001) – the latter result has also been corroborated using other protocols (Mackay, 1986; Tanaka & Yamazaki, 1990).

We used two different methods to estimate heritability. In the first assay, we calculated the heritability of fitness by conducting a 'within-generation' paternal half-sib analysis. This approach is commonly used by researchers because it avoids potential biases by maternal and dominance effects that may inflate estimates of additive genetic variance (Falconer & Mackay, 1996). However, this technique does not include the phenotypic variation that arises across generations (and genotype-by-environment interactions) due to factors such as culture medium heterogeneity (e.g. the level of desiccation and differences in which air-borne microbes colonize the culture medium; e.g. see Long & Rice, 2007). Thus, we also employed a 'cross-generational' parent–offspring regression method to measure individual fitness transmission between a dam and her daughters. Although this second estimate may potentially suffer from bias (i.e. include maternal effects), it does incorporate the differences in parental and offspring environments. Together, these assays both revealed that despite > 400 generations of adaptation to the laboratory environment, a high heritability of female adult fitness has persisted.

Materials and methods

Population history and culture protocol

In all experiments, we used *D. melanogaster* flies obtained from a wild-type population (LH_M) that has been reared, in large numbers (adult $n \geq 1792$ per generation), under standardized laboratory conditions for over 400 generations (described in detail in Rice *et al.*, 2005, 2006). Briefly, this discrete 14-day generation cycle is comprised of 'juvenile competition', 'adult competition' and 'oviposition' phases. In each generation, 56 'juvenile competition' vials are created by placing between 150 and 200 eggs into each vial that had been provisioned with 10 mL of cornmeal/molasses/killed yeast media. These vials are kept in an incubator (25 °C, 12-h light : 12-h dark cycle) until day 11.25 (post-egg deposition, with the first day designated as day '1') at which time the eclosed flies are collected under light CO_2 anaesthesia and mixed across vials. This extensive mixing generated gene flow between the different subpopulations derived from each of the 56 juvenile competition vials. From these flies, 56 sets of 'adult competition' vials are created, each consisting of 32 adult flies (16 males and 16 females) that are placed into vials containing fresh media and whose surface has been seeded with 6.4 mg (dry weight) of live yeast. The limited amount of live yeast generates strong scramble competition among females because yeast is the major factor limiting their fecundity (Rice *et al.*, 2005, 2006). The vials are returned for incubation for 48 h, whereupon flies are transferred (without anaesthesia) to new vials containing fresh media (but no live yeast). These 'oviposition vials' are returned for incubation for 48 h, after which time flies are discarded and the density of eggs in these vials (which become the juvenile competition vials for the subsequent generation) is manually culled until only 150–200 eggs remain. In this semelparous population, lifetime fecundity is easily measured by the number of eggs laid during the 18-h oviposition phase of the life cycle. This fecundity measure is an accurate assay of adult fitness because very few flies die as post-eclosion adults (Rice *et al.*, 2005, 2006). It is also a good index of total fitness because juvenile mortality is: (i) low (10–15% egg-to-adult mortality), (ii) uncorrelated with adult fitness and (iii) was found to be a minor contributor to total genetic fitness variation among genome-wide hemiclones derived from the LH_M population (Chippindale *et al.*, 2001; Rice *et al.*, 2005, 2006). All assays of fitness described below were designed to closely match the environmental conditions (e.g. culture density, medium and timing of the life cycle) encountered by the LH_M flies during their normal culture.

Within-generation estimation of the heritability of adult female fitness using paternal half-sib analysis

In the first assay, we conducted a 'within-generation' paternal half-sib analysis. In this assay, 25 males (sires) were each mated to four females (dams) each. Next, the variance in the lifetime fecundity of the progeny produced from these dams and sires was partitioned to estimate the additive genetic variation (and thus the heritability) for lifetime fecundity. The assay began with the collection of 25 adult males and 100 adult virgin females as they eclosed from the LH_M population on day 10 of their life cycle, which were kept in single-sex groups until day 11.25. At this time, 25 sets of one sire and four dams were created by randomly transferring one virgin male and four virgin females into vials containing 10 mL of media and 1.6 mg of live yeast added to the surface (to keep the per-female live yeast level at that typical of culture conditions) which were then kept in an incubator for 48 h. At that time, females were placed individually into vials containing fresh media without live yeast (and whose surface had been lightly scored) for 18 h before being discarded. The eggs laid by each female were immediately counted, and additional eggs (of the same age) were added to each juvenile competition vial to ensure that each contained a total of 180 eggs (matching the normal density of the LH_M population), before being returned to the incubator.

The supplemental eggs originated from a second laboratory population (LH_M-*bw*), with genetic background closely matching that of the LH_M population, except that a recessive brown-eyed marker allele (*bw*) has been introgressed through repeated back-crossing to LH_M. After 11.25 days, all adult flies were removed from each vial, counted and scored by eye colour, and from each vial of flies we created two (or, on rare occasions, only one) adult competition vials consisting of 16 brown-eyed males, three red-eyed females and 13 brown-eyed females, which were placed into vials containing culture medium and standard amounts of live yeast. These adult competition vials were maintained as above. Individual red-eyed females were then placed, respectively, into vials with fresh, scored, media and returned for incubation for 18 h later before being discarded, and the number of eggs in each vial was counted (a measure of each adult female's lifetime fecundity).

We used random effects ANOVA (REML) to divide the phenotypic variance of female fitness data into the between-sire, between-dam (nested within sires) and within-progeny components. We then estimated the heritability of adult female fitness based on the among-sire component of variation following the methods described in Falconer & Mackay (1996).

Cross-generation estimation of the heritability of adult female fitness using fitness of dams and their daughters

In the second assay, we estimated heritability of female lifetime fecundity using a 'cross-generational' parent–offspring regression method. We began by measuring the lifetime fecundity of 48 females from the LH_M population in each of five successive generations (for a total of $5 \times 48 = 240$ assayed females). We then used a subset of these females to carry out a mother–offspring regression. To increase experimental power (by increasing the variance in the independent variable), each generation we selected the five females with the highest, and the five with the lowest, lifetime fecundity for inclusion in a mother–offspring regression. We next measured the average lifetime fecundity of a sample of the offspring from each of these mothers, and used standard regression methods to estimate the heritability of lifetime fecundity.

This experiment began by randomly sampling flies from the LH_M population at the end of the juvenile competition phase of their life cycle (day 11.25 of the culture cycle) and created three adult competition vials (each containing 16 males and 16 females) in each of five consecutive generations. After 48 h in the incubator (the normal duration of the adult competition phase of the life cycle), flies were lightly anesthetized, and individual females were placed into 'oviposition' vials containing fresh media (the surface of which had been lightly scored). The eggs laid in the ensuing 18-h oviposition phase of the life cycle were counted. After measuring the lifetime fecundity of these $3 \times 16 = 48$ females (one vial per female) in each generation, we selected the five vials containing the most eggs (high maternal fitness) and the five vials containing the fewest eggs (low maternal fitness), for assays of offspring fitness. In order to ensure that variation in offspring fitness was not confounded by variation in larval density, we added LH_M-*bw* eggs (of the same age) to each of the 10 vials so that the final density of eggs per vial was 180. For clarity, the generation of flies assayed for maternal fitness will be referred to as the G1 flies, whereas the offspring produced from the highest and lowest fitness G1 females will be referred to as the G2 flies.

At the end of the juvenile competition phase of the G2's life cycle, all eclosed flies were sorted by sex and eye colour (red or brown) and tallied. Flies taken from each of these vials were used to create three G2 adult competition vials, which contained four red-eyed females (daughters from the G1 female that was assayed for adult fitness) and 12 brown-eyed competitor females. If a juvenile competition vial did not yield sufficient red-eyed females, a situation that was not uncommon in the 'low maternal fitness' group, a greater number of brown-eyed females were added to maintain a total of 16 females per vial. Sixteen males taken from the corresponding juvenile competition vial were also added to each of the three G2 adult competition vials. The ratio of red-eyed to brown-eyed males that were placed into in each G2 adult competition vial was matched (as closely as possible) to the ratio of red-eyed to brown-eyed males present in the G2 juvenile competition vial from which they were taken. At the end of the 48-h adult competition phase of the G2 generation, the adult fitness of the red-eyed daughters was measured by placing individual females into oviposition vials with fresh, scored, media and returned to the incubator. Eighteen hours later, all G2 adult flies were discarded, and the eggs laid by red-eyed females were counted in order to quantify female adult fitness. Fitness of G2 daughters was calculated by averaging the number of eggs laid by all of these females across the three replicate oviposition vials.

Although it was not the focus of this study, our experimental design also allowed us to measure fitness of sons from the high- and low-fitness dams. This was carried out by measuring the fraction of red-eyed offspring (sired by the sons of the assayed dams) among the progeny of the brown-eyed competitor females. G2 male fitness was calculated according to the following formula:

$$\frac{(\text{number of red-eyed offspring per brood})}{(\text{number of red-eyed adults placed into adult competition vial})} \times \frac{16}{\text{number of broods surveyed}}$$

averaged across the three replicate vials. This metric expresses male adult fitness in the same currency as was used to measure female adult fitness.

Our point estimate of the heritability of adult female fitness was two times the estimated slope from the bivariate regression of average adult fitness of daughters vs. the adult fitness of their mothers (using the software JMP v 7.0 2008; http://www.jmp.com/). Initially, we included block (generation of sampling) as a random factor into our model estimating slope. However, as it (and its interaction with maternal fitness) was a nonsignificant effect, it was not included in our statistical model. Bootstrap analysis (10 000 resamples) using the program STATISTICS101 (v 1.2.6 2008; http://www.statistics101.net) was used to calculate 95% confidence interval for our heritability estimate.

Results and discussion

In this study, we set out to examine the extent to which individual variation in lifetime adult fitness in female *D. melanogaster* was heritable in the context of a large, outbred, locally adapted laboratory population. Phenotypic variation in the lifetime fecundity of a random sample of 240 females was substantial (mean ± SD for female lifetime fecundity: 37.19 ± 13.48; Fig. 1). Using two independent techniques, we found evidence for a substantial heritability for adult female fitness.

First, our within-generation paternal half-sib assay revealed that much of the phenotypic variation in adult female fitness was attributable to genotype: total variance in female fecundity was 124.75, with 17.85 ± 8.03 (or 14.3 ± 6.4%) of that variance attributable to the contribution of the sires. The associated estimate of the heritability of adult fitness was 0.573 with a bootstrap 95% CI of 0.257–1.777. This heritability estimate of adult female fitness is similar to that of $h^2 = 0.53$ obtained by Pischedda & Chippindale (2006) using hemiclonal analysis (*reviewed in* Rice *et al.*, 2005) in a derivative population of LH_M that has been maintained separately since 2002.

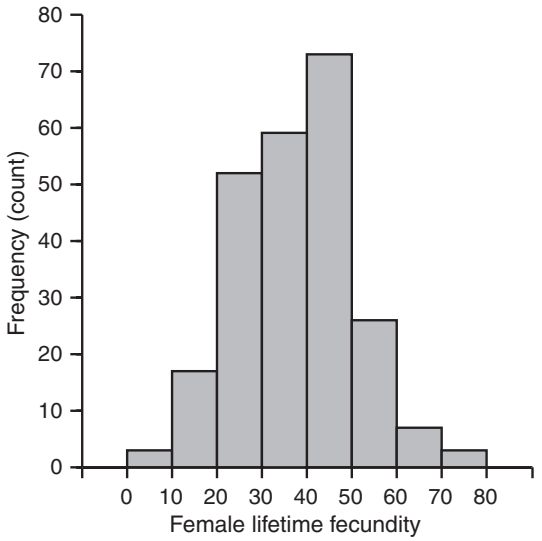

Fig. 1 Phenotypic distribution of adult lifetime fitness scores (measured as fecundity in the oviposition phase of the life cycle) for 240 adult *Drosophila melanogaster* females. The data conform closely with a normal distributed (Shapiro–Wilk's test; $W = 0.99$, $P = 0.24$).

Second, in our cross-generation parent–offspring assay, we found that a substantial proportion of the observed individual variation in the adult fitness of daughters was attributable to the fitness category (high or low) of their mothers (Fig. 2a). The lifetime fecundity of daughters from high-fitness mothers was, on average, 21% higher than that of the daughters from low-fitness mothers (mean lifetime fecundity of daughters ± SE: from high-fitness mothers = 37.84 ± 1.29, from low-fitness mothers = 31.17 ± 1.22; *t*-test: $t_{49} = 3.75$, $P < 0.0005$). Furthermore, there was a significant positive correlation between maternal and daughter adult fitness ($r = 0.52$, Pearson's correlation tests: $t_{49} = 4.27$, $P < 0.0001$, Fig. 2b). The slope (estimate ± SE) of the regression between the adult fitness of dams and their daughters was 0.203 ± 0.047, with a heritability estimate of 0.40 and 95% bootstrap (10 000 iterations) confidence interval of 0.2191–0.5587. This heritability estimate is potentially biased by maternal effects, but it nonetheless provides evidence that environmental variation across generations does not substantially negate the strong within-generation estimate of fitness heritability obtained from our within-generation paternal half-sib analysis. Interestingly, despite the substantial correlation between the adult fitness of mothers and daughters, we found no significant association between our measure of adult fitness of sons (relative number of offspring sired by these males among the brown-eyed competitor females) and that of their mothers (estimated slope ± SE = 0.015 ± 0.092, regression test of slope different from zero, $t_{49} = 0.126$, $P = 0.90$). Earlier work reported a negative correlation between adult male and female fitness of the same X chromosomes (Gibson *et al.*, 2002), the same genome-wide set of genes (hemiclone, Chippindale *et al.*, 2001) and between mothers and their sons (Pischedda & Chippindale, 2006). Our nonsignificant correlation does not reinforce the previous findings, but the large 95% confidence interval of the heritability estimate (−0.361 to 0.318, based on 10 000 bootstrap iterations) does not preclude a negative correlation.

Several factors could contribute to our high estimate of heritability for adult female fitness. One is that we measured adult fitness variation, rather than total fitness variation, and that negative correlations between fitness components might explain our high heritability estimate, i.e. our high heritability estimate would not apply to total fitness variation. As described in the Introduction, however, hemiclonal analysis of our LH_M population

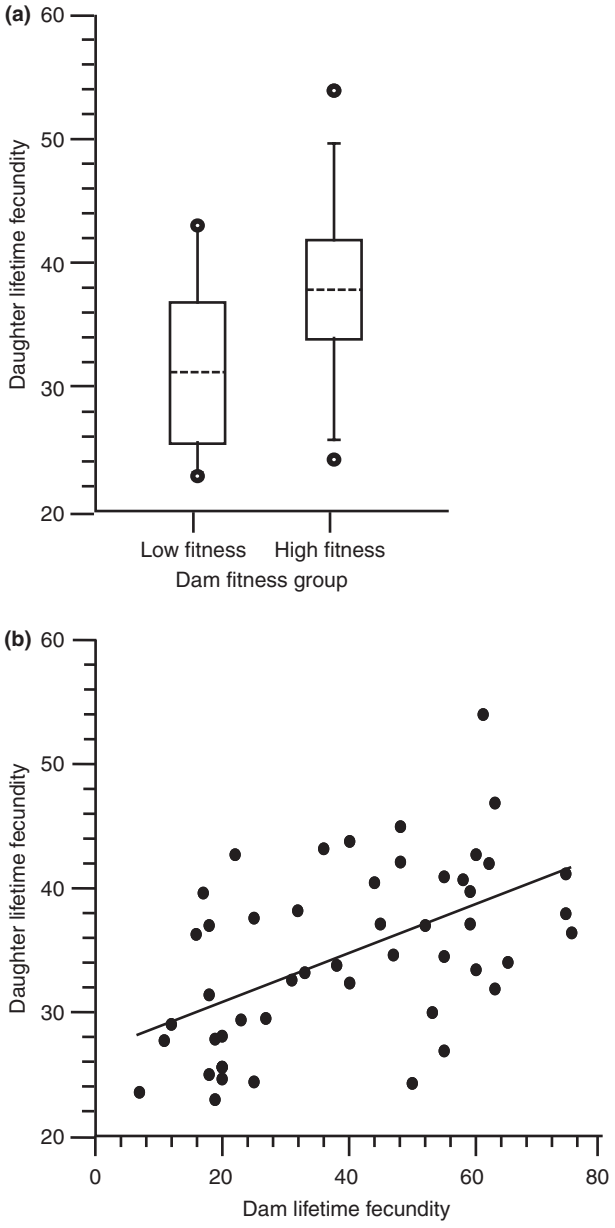

Fig. 2 (a) Adult lifetime fitness (measured as fecundity in the oviposition phase of life cycle) of *Drosophila melanogaster* females whose mothers came from 'high' and 'low' fitness groups. Box plots show the 19th, 25th, 75th and 90th percentiles, dots show data outside that range, and dashed lines indicate the mean values of each group. (b) Regression between the fitness scores of mothers and their daughters.

indicated that total variation in juvenile fitness is low, relative to that for adult fitness, and there is at most only a weak correlation between adult and juvenile fitness (Chippindale *et al.*, 2001; Rice *et al.*, 2005, 2006). As a consequence, a negative correlation between life-history stages is an unlikely explanation for the observed high heritability for adult female fitness. Nonetheless, there is an established negative correlation for adult fitness between the sexes (Chippindale *et al.*, 2001). We do not think that this correlation is a likely explanation for the observed high heritability for adult female fitness because such opposing selection is not predicted by theory to maintain substantial heritability for fitness (Kidwell *et al.*, 1977; Gavrilets & Rice, 2006).

Another factor that might contribute to our high estimate of heritability for adult female fitness is that of recent adaptation to a novel environment (Mayr, 1954; Templeton, 1980; López-Fanjul *et al.*, 2000). However, with over 400 generations to adapt to the new laboratory environment, most quantitative traits would have had ample time to shift by many standard deviations; so, a novel environment does not seem likely to be a complete explanation for the observed high heritability of adult fitness. Nonetheless, in order to maintain the lifetime fecundity of our LH_M base population at an average of 20–30 eggs per female, we have had to periodically (over the last 400 generations) reduce the amount of live yeast provided to females during the 'adult competition' phase of their life cycle. This anecdotal observation suggests that persistent adaptation to the laboratory environment may be a contributing factor maintaining high heritability for fitness in this population.

A final factor to consider is the fact that we had females laying eggs individually, rather than laying in groups of 16. This represents a departure from the normal culturing protocol of the LH_M population (creating a novel aspect to the environment) that is made necessary in order to measure fecundity of individual females. We cannot completely rule out the idea that this requisite departure from the normal culturing may have led to elevated heritable variation for adult female fitness. However, we have previously compared the fecundities of females housed individually or in groups of 16. We found mean fecundity to be the same in both treatments and their variances (of individually housed females or mean values of 16 females per vial) to follow the expected pattern of the variance of the mean values equalling the variance of the individual observations divided by the sample size (A.D. Stewart, unpublished data). This finding suggests, but certainly does not prove, that housing females singly during the oviposition phase of their life cycle is unlikely to modify female fitness in any substantial way.

Another class of explanations for the observed high heritability of adult female fitness is mutation–selection balance. Recent evidence suggesting that mutation–selection balance might plausibly maintain substantial fitness variation has come from empirical studies indicating high genome-wide mutation rates in *Drosophila* (Rifkin *et al.*, 2005; Haag-Liautard *et al.*, 2007), as well as from theoretical models that incorporate both real and apparent forms of stabilizing selection (Zhang *et al.*, 2004; Zhang & Hill, 2005). Although our LH_M population is

large and highly outbred, compared with most laboratory populations (about 1800 breeding adults produce each LH_M generation), it is nonetheless small compared with most natural populations and it experiences a more uniform environment. The more uniform environment is expected to gradually lead to lower standing genetic variation in our laboratory population (Gillespie & Turelli, 1989). The smaller population size will create higher levels of genetic drift, compared with larger natural populations, and act to reduce standing genetic variation maintained by mutation–selection balance. The rate of decay due to drift (per generation) is proportional to the reciprocal of $2N_e$; however, with an $N_e > 10^3$ and 400 generations of laboratory culture, genetic drift in our smaller laboratory population should not have eroded most of the variation maintained by mutation–selection balance.

Although we cannot unambiguously identify the factors contributing to our observed high level of heritable variation for fitness among adult females, our study suggests that after a major environmental change it is feasible for large outbred populations to maintain substantial levels of heritable genetic variation for a protracted period of time (i.e. hundreds of generations). As episodic factors, such as catastrophic fires, storms and flooding, as well as species invasions, natural (and human-induced) climate change and the red-queen process, are expected to cause all environments to continually change, the chronic lag load that these changes produce may be an important factor contributing to persistent heritability of net fitness in natural populations.

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