Sexual selection for rare beneficial mutations promotes the evolution of sexual reproduction and adaptation

Gilbert Roberts* and Marion Petrie[†]

***** Simonside Cottage, Morpeth, Northumberland, NE65 8RW, UK

Author for correspondence: gilbert.roberts@yahoo.co.uk

[†] Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK

Abstract

The evolution and widespread maintenance of sexual reproduction remains a conundrum in biology because asexual reproduction should allow twice the reproductive rate. One hypothesis is that sexual selection lessens the negative impact on fitness of accumulating deleterious mutations. However, for adaptation to occur, there must also be selection for beneficial mutations. Here we show that sexual selection can help explain the evolution and maintenance of sexual reproduction. In our model, females chose males with more beneficial mutations (as opposed to just fewer harmful ones) even when these occurred much more rarely. Sexual selection thereby increased fixation of beneficial mutations which increased the absolute genetic quality of sexual offspring. This increase in fitness relative to asexual offspring adds to the previously postulated effect of reduced mutation load in offsetting the cost of sex. Analysing our simulations reveals that female choice among males raised the fitness of reproducing males above that of females. We found that this effect could overcome the decline in average fitness that occurs when mutation rate increases, allowing an increase in the fixation of beneficial mutations. Sexual selection thereby not only facilitates the evolution of sexual reproduction but maintains sex by leveraging its benefits and driving adaptation.

Introduction

Any explanation for the evolution of sexual reproduction within groups must show how the production of males, even when they do not care for offspring, increases the fitness of sexually produced offspring, otherwise there is a 'two-fold cost of sex' [1, 2]. Sexual reproduction entails variance in mating success, especially where females can choose between males of varying quality and where a male can mate with more than one female [3, 4]. This differential mating success is integral to the process of sexual selection, which could theoretically contribute to the maintenance of sex by the selective removal of low quality males that effectively act as a sink for mutation load [5, 6]. Sexual selection could thereby reduce the risk of population extinction [7], as has been demonstrated in flour beetles *Tribolium castaneum* [8]. According to this theory, males become 'useful' in that females can pick those males with the lowest load of deleterious mutations.

Mutation is the source of variation and the overwhelming majority of mutations are deleterious [9] to the extent that models have ignored beneficial mutations, deeming them too rare to be of interest. Nevertheless, adaptation depends upon those rare occasions when mutations have a beneficial impact on fitness. Here, we investigate the role of sexual selection in favouring beneficial mutations. Sexual selection can be a powerful process resulting in strongly biased mating success [10]. This can even allow modifiers of the mutation rate ('mutator genes', such as factors controlling DNA repair [11, 12]) to persist, because female choice selects for those males with beneficial mutations [13, 14]. We postulate here that female choice can be so potent that it not only promotes the maintenance of genetic variation, but it allows beneficial mutations, despite their comparative rarity, to have a significant impact on fitness. This means that the two-fold cost of sex may be overcome not just by the lower reduction in fitness caused by deleterious mutation load [5, 6], but by the increase in fitness resulting from fixation of new beneficial mutations. We further postulate that female choice can favour an increase in mutation rate, despite the decline expected from the predominance of deleterious mutations, because female choice is effective in selecting for those with an increased number of beneficial mutations.

We simulated the 'genetic quality' of individuals by examining the evolution of deleterious and beneficial mutations in asexual and in sexual populations, and by varying the degree of female choice in the latter. Implicit in our model is the assumption that, in addition to determining survival, the mutations that a male accumulates determine the condition of some trait, which is used by female subjects in mate choice. Thus, we assume that a male's genetic quality is revealed in the trait and the female subjects use that information to select

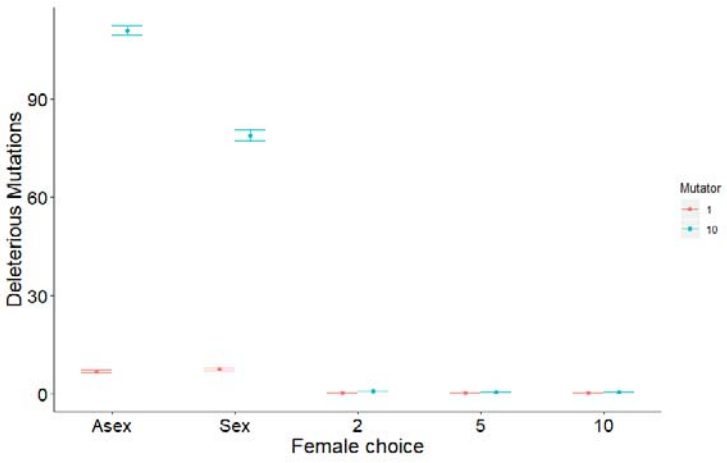
the best male. This assumption is supported by the literature on 'good genes' effects in sexual selection [15, 16] and by the demonstration that sexual traits can reveal genetic quality [17, 18]. It is also consistent with other sexual selection models [19]. We compared sexual and asexual populations in the presence of varying levels of sexual selection and a modifier of mutation rate. We hypothesized that increasing mutation rate above a baseline would leverage the effects of sexual selection making it more likely for sexual types to have higher genetic quality than asexual types. The rationale for this is that an increase in mutation rate feeds variation in genetic quality (and hence attractiveness), and that this variation promotes choice between males [4]. We consider that sexually reproducing individuals will vary in mating success [5] and that a key driver of this variation is female choice for high quality and attractive mates that will provide females with high viability and attractive offspring. We propose that females can actually get 'good genes' rather than 'fewer bad genes' as in the models of how sexual selection facilitates the evolution of sex [5, 6]. As such, we predicted that variability in mutation rate should facilitate the effect of sexual selection in overcoming the two-fold cost of sex.

Results

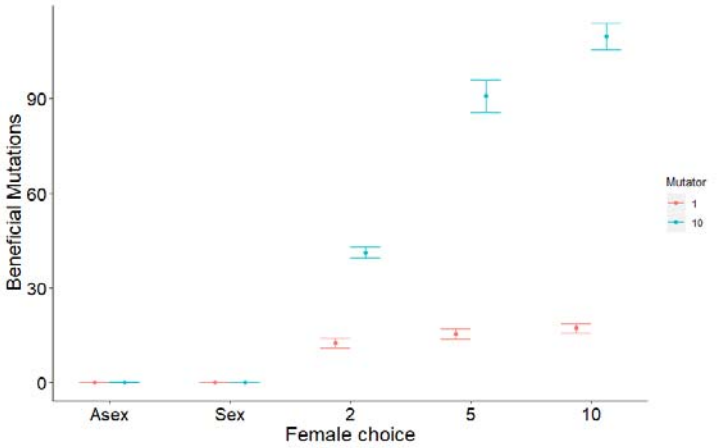
Looking at deleterious mutations first, we found that in populations with asexual reproduction and in those with sexual reproduction but no sexual selection, deleterious mutation load increased dramatically when mutation rate increased (Figure 1a). However, female choice, even between just two males, reduced deleterious mutations to very low levels. Female choice was so effective that even with a high mutation rate, the numbers of deleterious mutations were reduced to substantially below those found in asexual populations or in sexual populations lacking female choice. Conversely, numbers of beneficial mutations were low, even with a ten-fold increase in mutation rate in asexual populations and sexual ones without female choice (Figure 1b). However, with female choice, beneficial mutations were much more common, and increased mutation rate accentuated this effect. Summing these effects, overall genetic quality decreased with increasing mutation rate in asexual populations and sexual ones lacking female choice, yet it increased with increasing mutation rate in populations with female choice (Figure 1c). Thus, sexual selection was so powerful that it overcame the 1000-fold disadvantage of the beneficial mutation rate and allowed an increase in genetic quality with increased mutation rate. This increase in genetic quality occurred because sexual selection was effective at keeping numbers of deleterious mutations low despite an increase in mutation rate, yet was also effective in selecting for beneficial mutations, and could do this most effectively when mutation rate was high.

Figure 1

a



b



c

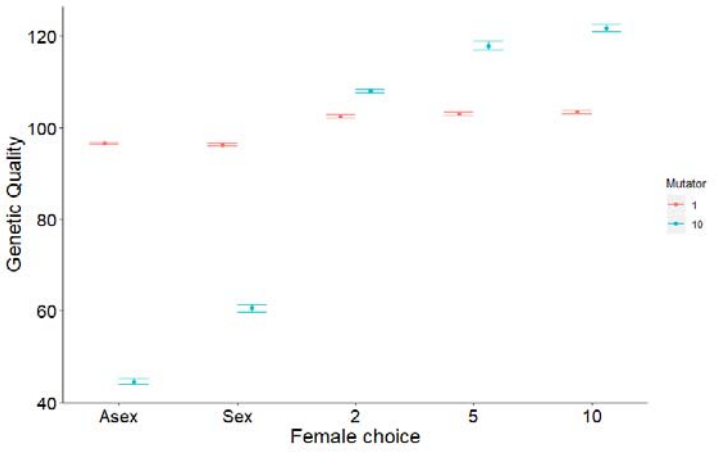


Figure 1 Legend

The figure shows how the numbers of mutations per individual vary with mode of reproduction and strength of female choice where “Asex” is asexual reproduction; “Sex” is sexual reproduction without female choice; and where “2”, “5” and “10” are sexual reproduction with female choice between the given number of males . Figures a and b show the numbers of mutations per individual; c shows ‘genetic quality’ calculated as baseline fitness (100) minus the number of deleterious mutations per individual multiplied by the effect of each (0.5); plus the number of beneficial mutations multiplied by the effect of each (0.2). The rate of deleterious mutations per gene per individual per generation was 1000x that of beneficial mutations. Plotted are the means and standard errors computed across 10 simulations for each set of parameters, taken at generation 1000. Plotted in red are the results where the mutator gene $M = 1$; blue is where $M = 10$, i.e. the rates of both deleterious and beneficial mutations are at 10x the baseline mutation rates, which were 10^{-3} and 10^{-6} respectively. Other parameters: population size N=1000, equally divided between males and females in simulations with sexual reproduction; cost of female choice = 0.02*female choice.

We further investigated the interaction between female choice and mutation rate (Figure 2). Genetic quality increased with mutation rate and female choice to an intermediate maximum before declining rapidly. High levels of female choice improved genetic quality; but there came a point where even the highest level of female choice shown was insufficiently powerful not to be overwhelmed by the surge in deleterious mutations caused by a substantially increased mutation rate.

Figure 2.

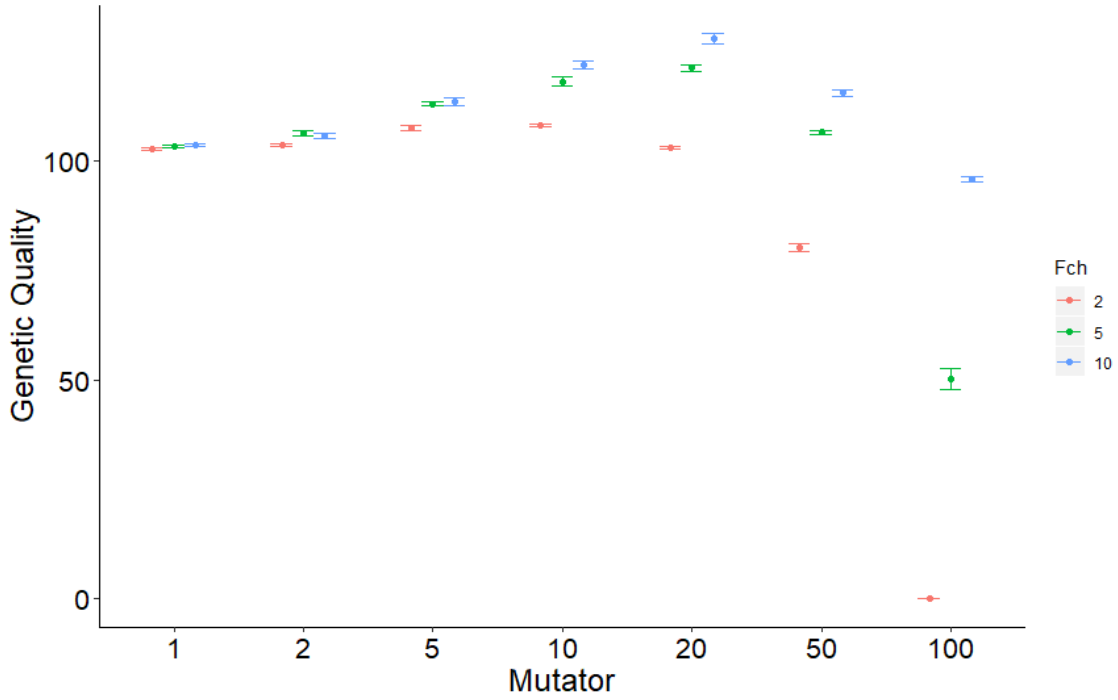


Figure 2 Legend.

The figure shows how 'genetic quality' varies with a 'Mutator' and with sexual selection by female choice. Genetic quality was calculated as given in Fig. 1. The mutator was a multiplier of the default mutation rates. Female choice was between 2, 5 and 10 males. Plotted are the means and standard errors computed across 10 simulations for each set of parameters, taken at generation 1000. Other parameters were as in Fig. 1.

We investigated the robustness of our results by varying key parameters whilst maintaining a moderate degree of female choice (F = 5). First, we varied the ratio of deleterious to beneficial mutation around the default ratio of 1000:1 respectively. As intuitively expected, genetic quality increased as beneficial mutations became relatively more common, and especially when this factor combined with a higher mutation rate (Figure S1). Looking at the effect on genetic quality of each beneficial mutation, we can again see that the results are intuitive (Figure S2): increasing the effect of beneficial mutations increases genetic quality, especially when mutation rate is high. Varying the cost of female choice within the range shown has no effect on genetic quality in either mutation rate condition (Figure S3). Increasing the population size, P, increased the effect size, as expected from the increased potential for genetic change across more individuals (Figure S4). Varying recombination rate had a little quantitative effect, with increased recombination allowing an increase in genetic quality, presumably through allowing favourable genetic combinations (Figure S5). All in all, varying key parameters suggested that the main effect we describe was robust.

The benefit of simulations is that they can help us predict processes that are difficult to comprehend intuitively or mathematically; the corollary is that they can be hard to interpret. To better understand the processes in the model we hypothesized that female choice selects for a breeding population that results in offspring that are s standard deviations above the mean of the underlying population. To test whether males that were chosen to breed were indeed of higher genetic quality than the population from which they were drawn, we aggregated across the first 1000 generations for all 1000 reproducing pairs and calculated the mean difference in genetic quality between females and their chosen males. Where female choice was absent and mutation was at the default rate, the mean difference was 0.01 ± <0.005 (standard error of the mean); with females choosing the best of 10 males and mutation rate at 10x the default, the difference was 0.22 ± <0.005. Therefore, females were choosing males that had a genetic quality equivalent to approximately 1 beneficial mutation above the average (recall that we modelled only a few genes, not the entire genome). In this way, sexual selection appears to be able to exploit increasing variation caused by increased mutation rate and actually produce an increase in genetic quality out of a background that one would otherwise expect to be dominated by increased deleterious mutation load.

As a simple analytical approximation, consider that female choice between males results in offspring that are s standard deviations above the mean. For the cost of sex to be overcome we then need:

$$\bar{x} + s\sigma > 2\bar{x}$$

$$s > \frac{\bar{x}}{\sigma}$$

Equation 1

This equation will most readily be satisfied when the standard deviation of the genetic quality is high relative to the mean. That is, there should be high variability within the population. Variability results from mutation, and we can show when an increase in mutation rate can be favoured. This can occur when the decrease in the mean genetic quality in the population that necessarily results from an increase in mutation rate (assuming there is a strong predominance of deleterious over beneficial mutations) is more than compensated for by the effect of female choice in selecting for males of high genetic quality. If subscripts 1 and 2 indicate the means and standard deviations before and after the change in mutation rate, then:

$$\bar{x}_2 + s\sigma_2 > \bar{x}_1 + s\sigma_1$$

$$s > \frac{\bar{x}_1 - \bar{x}_2}{\sigma_2 - \sigma_1}$$

Equation 2

This analytical approach has the benefit that it considers the whole genome, something we do not attempt in our simulations, which allow us to include stochastic factors at the level of the gene. As a hypothetical numerical example, consider that increasing the mutation rate lowers the mean genetic quality from 1 to 0.9 whilst increasing the variance in genetic quality from 0.2 to 0.4. Consider also that female choice selects for males that produce offspring 1 standard deviation above the mean. Entering these hypothetical values into Equation 2 demonstrates that an increase in mutation rate combined with female choice can indeed lead to an increase in the genetic quality of offspring. To aid understanding, this example is illustrated in Figure S6. Whilst simplified, this makes the point that an increase in mutation rate can be favoured under sexual selection and can thereby contribute to overcoming the two-fold cost of sex.

Discussion

We have shown here that an increase in mutation rate works with sexual selection to increase genetic quality and thereby assist in overcoming the two-fold cost of sex. Crucially, our simulations reveal that sexual selection not only leads to the maintenance of variation [13, 20], but also leads to an adaptive increase in genetic quality. This is counterintuitive

given that any increase in mutation rate brings 1000 times as many deleterious as beneficial mutations in our model. This result highlights just how powerful the effect of female choice can be, even when just choosing between 2 males. We believe this is the first time that this effect has been reported. Its significance is that if mutation rate is elevated above a typically postulated minimum level then this would increase the benefits of sex relative to asexual reproduction, helping to overcome what has been termed the 'two-fold cost of sex' [1, 2]. It therefore seems that the role of sexual selection in the promotion of heritable genetic variation is key to understanding the evolution of sexual reproduction.

Our model assumes that mutation can be controlled genetically. One mechanism for this is through selection on those genes that are responsible for DNA repair [11]. We predict a greater mutation rate in genes that influence sexually selected phenotypes and in more sexually selected species. Across non-human species, particularly in birds, which differ in within population variance in mating success [21], and thus the level of sexual selection, there is some evidence of a positive correlation with the rate of mutation, measured by variance in minisatellite mutation rate [22, 23]. Given that sexual selection can often result in greater variance in mating success in males, our results are also consistent with male-biased mutation rates [24]. Our results may also be consistent with the finding that sexual selection interacts with mutation rates in seed beetles [25].

Our model reveals a positive feedback effect whereby a high mutation rate can favour sexual reproduction over asexual reproduction, while sexual reproduction with sexual selection can favour a high mutation rate. We speculate that this creates a ratchet effect in that once sexual reproduction is established, it becomes harder to switch back to asexual reproduction. Paradoxically, natural selection will tend to favour a low mutation rate [9], yet adaptation requires mutation. Our model shows how a faster rate of adaptation can occur with sexual selection. This is consistent with the finding that sexual selection (measured as the degree of polygyny) interacts with the rate of molecular evolution and with body mass to predict species richness at the genus level [26]. We argue that evolvability itself is under selection [27], and that through sexual reproduction with sexual selection, evolution can lead to greater evolvability.

Methods

We simulated the 'genetic quality' of individuals by examining the evolution of deleterious and beneficial mutations in asexual and in sexual populations, and by varying the degree of female choice in the latter. A simplified flow diagram of the simulations is given in Figure S6 and a Visual C program is provided as supplementary information. Our simulation methods were based on models of the evolution of mutation rate [11, 13]. As in those simulations, the parameters reflected literature estimates where available [28], subject to the constraint that the model was intended as a simple abstraction of reality and not an attempt to simulate an entire genome.

The simulations began by setting up a population of *P* individuals. In simulations of sexual populations, half were male and half female. Individuals were given a pair of homologous 'chromosomes' (i.e., we assumed diploidy) each bearing a 'mutator gene' and an associated string of 10 'viability genes'. We did not assume that these genes constituted the entire genome; only that there were no interactions between the genes of interest and those at other sites and that for the purposes of comparison between simulations, all other things were equal.

Each viability gene was subjected to a mutation process in which the rates of deleterious and beneficial mutations varied between simulations. The absolute rates of mutation were determined by the mutator gene, which increased the rates of beneficial and of deleterious mutation by a factor *M*. We assumed that the mutator gene affected DNA repair only in a relatively small region of the genome [29], namely the set of viability genes referred to above; that it was adjacent to the first of the row of viability genes; and that the crossover rate between the mutator and the first viability gene was the same as between each other viability gene.

Individuals were subjected to a mortality process, whereby their probability of survival was a function of their genetic quality. Deleterious mutations were assumed to have larger phenotypic effects than beneficial mutations: deleterious mutations reduced the wild type fitness of 100 by 0.5; beneficial mutations increased it by 0.2. The model assumed co-dominance with additive fitness effects, so the effects of mutations were summed to give 'genetic qualities', which determined individual survivorship in a mortality process.

Surviving individuals reproduced, either by asexual or by sexual reproduction, the latter with or without female choice. Asexual reproduction was by selecting an individual at random and

copying its chromosomes into an individual in the next generation. Sexual reproduction without female choice involved selecting a male and a female subject at random. In the case of female choice, a female subject was selected at random, and a set of *F* male subjects was selected at random. The female then bred with the male of highest genetic quality from that set of *F* males. This 'best of n' rule is the most widely used rule in modelling female choice [30, 31] and has some empirical support from lekking species [32]. For each sexual mating, one offspring was produced by bringing together chromosomes contributed by both parents. This was carried out by selecting a chromosome at random from each parent and allowing crossover between each adjacent gene with probability 0.01. The process of selecting parents and producing offspring was repeated until the population was replaced by a new generation of *P* individuals.

Unless otherwise stated, parameters used were as given in Table S1.

Author contributions: GR devised the computer simulations and analysis and wrote the paper. MP conceived the original idea of relating sexual selection and mutation rate, and contributed to the theoretical background.

Acknowledgements: [none]

References

1. Lehtonen, J., M.D. Jennions, and H. Kokko, *The many costs of sex.* Trends in Ecology & Evolution, 2012. **27**(3): p. 172-178.
2. Maynard Smith, J., *What use is sex?* Journal of Theoretical Biology, 1971. **30**(2): p. 319-335.
3. Trivers, R.L., *Parental investment and sexual selection*, in *Sexual selection and the descent of man 1871-1971*, B. Campbell, Editor. 1972, Aldone: Chicago. p. 136-179.
4. Petrie, M. and M. Lipsitch, *Avian polygyny is most likely in populations with high variability in heritable male fitness.* Proceedings of the Royal Society of London. Series B: Biological Sciences, 1994. **256**(1347): p. 275-280.
5. Agrawal, A.F., *Sexual selection and the maintenance of sexual reproduction.* Nature, 2001. **411**(6838): p. 692-695.
6. Siller, S., *Sexual selection and the maintenance of sex.* Nature, 2001. **411**(6838): p. 689-692.
7. Whitlock, M.C., *Fixation of new alleles and the extinction of small populations: drift load, beneficial alleles, and sexual selection.* Evolution, 2000. **54**(6): p. 1855-1861.

8. Lumley, A.J., et al., *Sexual selection protects against extinction.* Nature, 2015. **522**(7557): p. 470-473.
9. Charlesworth, D., N.H. Barton, and B. Charlesworth, *The sources of adaptive variation.* Proceedings of the Royal Society B: Biological Sciences, 2017. **284**(1855): p. 20162864.
10. Clutton-Brock, T., *Reproductive competition and sexual selection.* Philosophical Transactions of the Royal Society B: Biological Sciences, 2017. **372**(1729): p. 20160310.
11. Taddei, F., et al., *Role of mutator alleles in adaptive evolution.* Nature, 1997. **387**(6634): p. 700-702.
12. Agrawal, A.F. and A.D. Wang, *Increased Transmission of Mutations by Low-Condition Females: Evidence for Condition-Dependent DNA Repair.* PLOS Biology, 2008. **6**(2): p. e30.
13. Petrie, M. and G. Roberts, *Sexual selection and the evolution of evolvability.* Heredity, 2007. **98**(4): p. 198-205.
14. Dugand, R.J., W.J. Kennington, and J.L. Tomkins, *Evolutionary divergence in competitive mating success through female mating bias for good genes.* Science Advances, 2018. **4**(5): p. eaaq0369.
15. Petrie, M., *Improved growth and survival of offspring of peacocks with more elaborate trains.* Nature, 1994. **371**(6498): p. 598-599.
16. Møller, A.P. and R.V. Alatalo, *Good-genes effects in sexual selection.* Proceedings of the Royal Society of London. Series B: Biological Sciences, 1999. **266**(1414): p. 85-91.
17. David, P., et al., *Condition-dependent signalling of genetic variation in stalk-eyed flies.* Nature, 2000. **406**(6792): p. 186-188.
18. Hale, M.L., et al., *Is the peacock's train an honest signal of genetic quality at the major histocompatibility complex?* Journal of Evolutionary Biology, 2009. **22**(6): p. 1284-1294.
19. Kokko, H., et al., *The sexual selection continuum.* Proceedings of the Royal Society of London. Series B: Biological Sciences, 2002. **269**(1498): p. 1331-1340.
20. Kotiaho, J.S., et al., *On the resolution of the lek paradox.* Trends in Ecology & Evolution, 2008. **23**(1): p. 1-3.
21. Petrie, M. and B. Kempenaers, *Extra-pair paternity in birds: explaining variation between species and populations.* Trends in Ecology & Evolution, 1998. **13**(2): p. 52-58.
22. Møller, A.P. and J.J. Cuervo, *Minisatellite mutation rates increase with extra-pair paternity among birds.* BMC Evolutionary Biology, 2009. **9**(1): p. 100.

23. Anmarkrud, J.A., et al., *Factors affecting germline mutations in a hypervariable microsatellite: A comparative analysis of six species of swallows (Aves: Hirundinidae).* Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 2011. **708**(1): p. 37-43.
24. Ellegren, H., *Characteristics, causes and evolutionary consequences of male-biased mutation.* Proceedings of the Royal Society B: Biological Sciences, 2007. **274**(1606): p. 1-10.
25. Baur, J. and D. Berger, *Experimental evidence for effects of sexual selection on condition-dependent mutation rates.* Nature Ecology & Evolution, 2020.
26. Iglesias-Carrasco, M., et al., *Sexual selection, body mass and molecular evolution interact to predict diversification in birds.* Proceedings of the Royal Society B: Biological Sciences, 2019. **286**(1899): p. 20190172.
27. Earl, D.J. and M.W. Deem, *Evolvability is a selectable trait.* 2004.
28. Drake, J.W., et al., *Rates of Spontaneous Mutation.* Genetics, 1998. **148**(4): p. 1667.
29. Metzgar, D. and C. Wills, *Evidence for the Adaptive Evolution of Mutation Rates.* Cell, 2000. **101**(6): p. 581-584.
30. Janetos, A.C., *Strategies of female mate choice: A theoretical analysis.* Behavioral Ecology and Sociobiology, 1980. **7**(2): p. 107-112.
31. Johnstone, R.A. and D.J.D. Earn, *Imperfect female choice and male mating skew on leks of different sizes.* Behavioral Ecology and Sociobiology, 1999. **45**(3): p. 277-281.
32. Petrie, M., T. Halliday, and C. Sanders, *Peahens prefer peacocks with elaborate trains.* Animal Behaviour, 1991. **41**(2): p. 323-331.