BRIEF COMMUNICATIONS

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MALE-BIASED MUTATION, SEX LINKAGE, AND THE RATE OF ADAPTIVE EVOLUTION

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Abstract.—An interaction between sex-linked inheritance and sex-biased mutation rates may affect the rate of adaptive evolution. Males have much higher mutation rates than females in several vertebrate and plant taxa. When evolutionary rates are limited by the supply of favorable new mutations, then genes will evolve faster when located on sex chromosomes that spend more time in males. For mutations with additive effects, Y-linked genes evolve fastest, followed by Z-linked genes, autosomal genes, X-linked genes, and finally W-linked and cytoplasmic genes. This ordering can change when mutations show dominance. The predicted differences in substitution rates may be detectable at the molecular level. Male-biased mutation could cause adaptive changes to accumulate more readily on certain kinds of chromosomes and favor animals with Z-W sex determination to have rapidly evolving male sexual displays.

Key words.—Male-driven evolution, sex-biased mutation, sex chromosomes, sexual selection, substitution rate.

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A large and growing body of data shows that males often have substantially higher mutation rates than females (Hurst and Ellegren 1998; Li et al. 2002). When mutation is male-biased, genes that spend more time in males than females tend to have higher mutation rates. This causes sex linkage to influence rates of neutral molecular evolution (Miyata et al. 1987, 1990). The same effect could also have important implications for rates of adaptive evolution when mutations favored by positive selection are limiting. We might anticipate that the most rapidly evolving will be genes on the Y chromosome (which are always carried in males), followed by Z-linked genes (as in birds and Lepidoptera, which have ZZ males and ZW females), autosomal genes, X-linked genes (as in mammals, which have XY males and XX females), and finally W-linked and cytoplasmic genes.

The ratio of male to female mutation rates, α, is often 5.0 or larger. Estimates of α range from 1.8 to 8.5 in mammals and from 1.8 to 6.5 in birds (Hurst and Ellegren 1998; Li et al. 2002). In salmonid fish, α is estimated to be between 5.35 and 6.6 (Ellegren and Fridolfsson 2003). Male-biased mutation has also been found in plants (Filatov and Charlesworth 2002; Whittle and Johnston 2002). The only example of female-biased mutation we are aware of is at a microsatellite locus in a sea turtle (Hoekeert et al. 2002). Sex-biased mutation has not been found in other groups, including *Drosophila* (Bauer and Aquadro 1997), and it is not clear at present what the taxonomic distribution of the phenomenon is.

This paper presents a simple model for substitution rates of sex-linked and autosomal genes evolving under positive selection when there is sex-biased mutation. The results show sex-biased mutation can cause the pattern of a gene's inheritance to have substantial effects on its rate of adaptive evolution. We discuss how the predictions might be tested at the molecular level and how sex-biased mutation may affect several evolutionary phenomena.

THE MODEL

Our basic model is a straightforward extension of Charlesworth et al. (1987), who studied the effects of sex linkage on evolutionary rates when mutation rates are not sex-biased. The model is laid out in Table 1. The substitution rate for a gene under positive selection is determined by the product of two factors: the flux of favorable new mutations into the population, and the probability that a new mutation is fixed. First, the mode of inheritance affects the flux of new mutations at a locus because it changes the number of gene copies carried by the two sexes. For example, in a population with size N and an even sex ratio, an X-linked gene has N copies available to mutate in females, but only $N/2$ available in males. The mutation fluxes shown in columns 2 and 3 of Table 1 are expressed in terms of v, the mutation rate in females.

Second, the mode of inheritance affects fixation probabilities through its impact on the fraction of time loci spend in males and females (where they may be under different selection pressures) and whether they appear in a diploid or hemizygous state. Consider, for example, genes that affect only male fitness. All copies of a Y-linked mutation are under selection, but only one-third of X-linked mutations are. We calculated fixation probabilities assuming dosage compensation (that is, genes have the same fitness effects when hemizygous as when homozygous) using equation 3 from Charlesworth et al. (1987). The results shown in Table 1 are expressed in terms of the selective advantage s of a mutant homo- or hemizygote and the dominance coefficient h (where $h = 1/2$ implies no dominance). We confirmed the accuracy of these results by numerical analysis of a branching process model (Charlesworth et al. 1987), which shows the error in approximations for fixation probabilities shown in Table 1 is typically less than 10%.

Finally, the substitution rates are simply the product of the total flux of mutations and the fixation probability. The results, given in Table 1, show that the mode of inheritance

TABLE 1. Effects of the mode of inheritance on substitution rates.

Mode of inheritance	Flux from males	Flux from females	Male-limited trait		Female-limited trait		Expressed in both sexes	
			Fixation probability	Substitution rate	Fixation probability	Substitution rate	Fixation probability	Substitution rate
Autosomal	$Nv\alpha$	Nv	hs	$Nv(\alpha + 1)hs$	hs	$Nv(\alpha + 1)hs$	$2hs$	$2Nv(\alpha + 1)hs$
X	$\frac{1}{2}Nv\alpha$	Nv	$\frac{2}{3}s$	$\frac{1}{3}Nv(\alpha + 2)s$	$\frac{4}{3}hs$	$\frac{2}{3}Nv(\alpha + 2)hs$	$\frac{2}{3}(2h + 1)s$	$\frac{1}{3}Nv(\alpha + 2)(1 + 2h)s$
Y	$\frac{1}{2}Nv\alpha$	0	$2s$	$Nv\alpha s$	—	—	—	—
Z	$Nv\alpha$	$\frac{1}{2}Nv$	$\frac{4}{3}hs$	$\frac{2}{3}Nv(2\alpha + 1)hs$	$\frac{2}{3}s$	$\frac{1}{3}Nv(2\alpha + 1)s$	$\frac{2}{3}(2h + 1)s$	$\frac{1}{3}Nv(2\alpha + 1)(1 + 2h)s$
W	0	$\frac{1}{2}Nv$	—	—	$2s$	Nvs	—	—
Cytoplasmic	0	$\frac{1}{2}Nv$	0	0	$2s$	Nvs	$2s$	Nsv

has substantial effects. The results for Y-linkage, W-linkage, and cytoplasmic inheritance should be treated with great caution because of the effects of selection acting on linked loci in these nonrecombining genomes (see Charlesworth and Charlesworth 2000). We therefore focus on X- and Z-linkage in the rest of this paper.

It is convenient to compare the substitution rates by standardizing them relative to the rate under autosomal inheritance. This comparison assumes that the parameters for new mutations (s, h, and v) are on average equal for the different modes of inheritance. Figure 1 shows the effect of male-biased mutation on the relative substitution rates for additive mutations on X and Z chromosomes ($h = 1/2$). With a mutation bias of $\alpha = 5$, for example, Z-linked genes evolve 22% faster and X-linked genes 22% slower than their autosomal counterparts.

The relative substitution rates are sensitive to the dominance of new mutations. This is seen in Figure 2, which shows the rates for genes selected in both sexes, standardized to autosomal loci with additive mutations ($h = 1/2$). When mutation is not sex-biased, X- and Z-linked loci selected in both sexes have higher substitution rates than autosomal loci whenever alleles are partially recessive ($h < 1/2$; Charlesworth et al. 1987). When there is sex-biased mutation, however, the conditions are changed. With $\alpha = 5$, X-linked genes evolve faster only when mutations are quite recessive ($h < 7/22 \approx 0.32$), whereas Z-linked genes are faster over a broad range of dominance values ($h < 11/14 \approx 0.79$).

Table 2 and Figure 3 show the maximum value of h that causes X-linked and Z-linked genes to evolve faster than their autosomal counterparts as a function of the bias α. The results depend on whether the mutations are selected in one or both sexes. When advantageous mutations are selected in both sexes, Z-linked loci evolve more rapidly than autosomal loci over the broadest range of dominance values, whereas X-linked loci evolve more rapidly under the narrowest range. Cases in which selection acts only on one sex are interme-

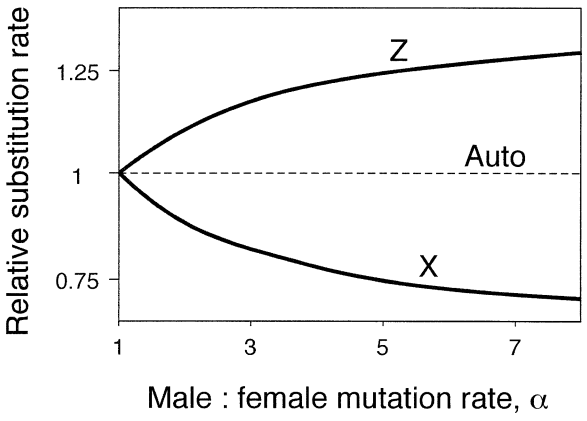

FIG. 1. Effects of sex-biased mutation on substitution rates of Z- and X-linked loci relative to autosomal loci. Additive fitness effects ($h = 1/2$), dosage compensation, and equal selection on both sexes are assumed.

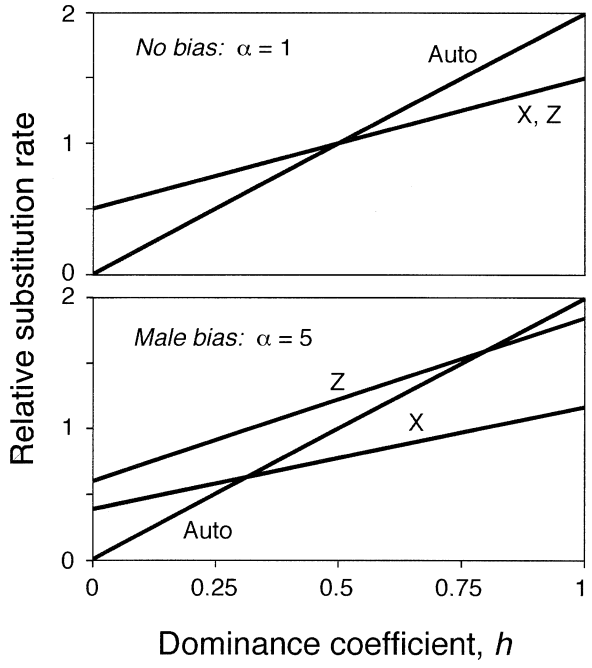

FIG. 2. Effects of dominance on the substitution rates with and without male-biased mutation. Rates are scaled relative to an autosomal locus with additive mutations ($h = 1/2$), and equal selection on both sexes is assumed.

TABLE 2. Conditions for higher substitution rates of X- and Z-linked loci relative to autosomal loci.

	Selected sex		
	Males only	Females only	Both sexes
Autosome < X	$h < \frac{2 + \alpha}{3(1 + \alpha)}$	$\alpha < 1$	$h < \frac{2 + \alpha}{2(1 + 2\alpha)}$
Autosome < Z	$1 < \alpha$	$h < \frac{1 + 2\alpha}{3(1 + \alpha)}$	$h < \frac{1 + 2\alpha}{2(2 + \alpha)}$

diate. Two situations are not shown in Figure 3: X-linkage when selection acts only on females, and Z-linkage when selection acts only on males. The dominance coefficient has no effect in these cases: the relative substitution rate for X-linked genes is higher whenever mutation is female-biased ($\alpha < 1$), whereas for Z-linked genes it is higher whenever mutation is male-biased ($\alpha > 1$).

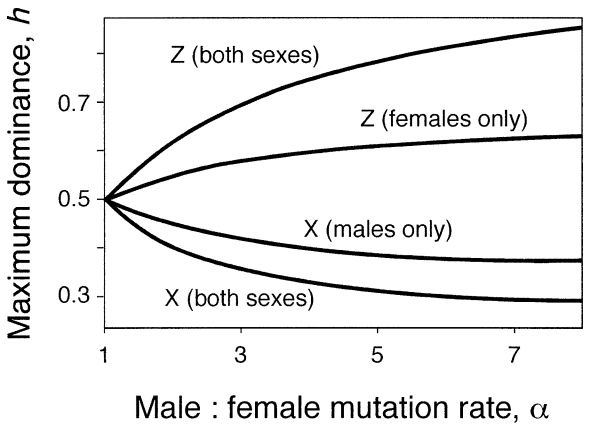

FIG. 3. The maximum dominance coefficient *h* that causes Z- and X-linked loci to evolve faster than comparable autosomal loci, as a function of the mutation bias α.

DISCUSSION

Sex biases in mutation rates can substantially alter the substitution rates of sex-linked loci relative to autosomal genes under positive selection. When favorable mutations have additive effects, male-biased mutation will cause Z-linked loci to evolve faster and X-linked loci slower than autosomal genes (Fig. 1).

The consequences of sex linkage for evolutionary rates may be relevant to many loci and many phenotypic traits. Although sex chromosomes typically represent only a small fraction of the genome, in some taxa they appear to carry a disproportionate amount of the genetic variation. Reinhold's (1998) review of male display traits in mammals and insects drew the striking conclusion that typically one-third of all phenotypic variation is X-linked. The Y chromosome of *Drosophila melanogaster* contributes 68% as much genetic variance to lifetime fitness in males as an entire X/autosome haplotype (Chippindale and Rice 2001). Prowell (1998) surveyed the data on Lepidoptera and found that 60% of traits with sex-limited expression and 29% of traits expressed in both sexes are Z-linked. Sex linkage of plumage traits involved in species recognition has recently been described in birds (Saetre et al. 2002). However, Ritchie and Phillips (1998) did not find evidence for disproportionate representation of sex-linked genes for traits involved in premating isolation of insects outside of the Lepidoptera and perhaps the Orthoptera.

Our results suggest that genes on different kinds of chromosomes may differ on average in their nonsynonymous substitution rates. A second approach to testing the predictions of the model is to ask whether there is a tendency for adaptive divergence between populations or species to map frequently to the Z chromosomes and rarely to the X. The high frequency with which interspecific genetic differences map to the Z in Lepidoptera (Prowell 1998) is consistent with the prediction.

Two mechanisms could cause male-biased mutation to lead to the overrepresentation of Z-linked loci, and underrepresentation of X-linked loci, in adaptive divergence. First, loci already on these chromosomes will have different substitution rates, as described above. Second, there is a weak evolutionary force that might favor the accumulation of rapidly evolving loci on the Z and their depletion from the X. When loci are duplicated on different chromosomes, copies with faster rates of adaptive evolution may tend to survive and those with slower rates be lost. Current evidence, however, does not support this second suggestion. Male-expressed genes are overrepresented on the X in mice (Wang et al. 2001) and humans (Lercher et al. 2003), and both rodents and primates show male-biased mutation (Hurst and Ellegren 1998; Li et al. 2002). In contrast, male-expressed genes are underrepresented on the X in *Drosophila* (Parisi et al. 2003), and there has been a net flux of genes from the X to the autosomes (Betrán et al. 2002). Although these last two observations are consistent with the prediction, there is not evidence for male-biased mutation in flies (Bauer and Aquadro 1997).

Male-biased mutation may have consequences for sexually selected traits. Male sexual displays are among the most rapidly evolving traits (Darwin 1871), suggesting they are often under strong positive selection. If other factors (i.e., *N*, *h*, *s*, and *v*) do not vary systematically between two groups, then the one with ZW sex determination may tend to have faster-evolving sexual displays than the one with an XY system (since genetic variation for male displays is typically X-linked, not Y-linked; Reinhold 1998). Perhaps this effect accelerates the evolution of displays in birds and butterflies relative to groups such as mammals and flies, and contributes to their propensity for bright and sexually dimorphic coloration.

Male-biased mutation may also have implications for understanding the ''large-X effect,'' the observation that X-linked genes often play a role in determining male fitness in hybrid crosses (Coyne and Orr 1989). Several ideas have been suggested to explain this pattern (reviewed by Turelli and Orr 2000). One is the ''faster-X'' hypothesis, which proposes that X-linked genes evolve faster than autosomal genes on average. When males and females have equal mutation rates, positive selection will cause X-linked genes to have higher substitution rates if favorable mutations are partly recessive ($h < 1/2$; Charlesworth et al. 1987). With male-biased mutation, however, the conditions are more restrictive: favorable

mutants must be quite recessive (Fig. 3). This decreases the scope that the faster-X mechanism has for contributing to the large-X effect. Conversely, male-biased mutation should enhance the contribution that Z chromosomes make to postzygotic isolation.

Evolution of the Y and W chromosomes may be also be affected by sex-biased mutation. Several evolutionary processes, involving both deleterious and advantageous mutations, are thought to contribute to the degeneration of nonrecombining sex chromosomes (reviewed in Charlesworth and Charlesworth 2000). In general, a nonrecombining neo-Y or neo-W is expected to decline in fitness more rapidly with higher rates of mutation to both advantageous and deleterious alleles. Hence, male-biased mutation is expected to cause a neo-Y chromosome to degenerate more rapidly than a neo-W.

It is unclear why mutation is male biased. A leading hypothesis has been that there are more cell divisions, and hence more rounds of DNA replication, preceding meiosis leading to sperm than to those leading to eggs (Haldane 1935). Some observations, however, are difficult to reconcile with that idea (Hurst and Ellegren 2002; Li et al. 2002). Whatever the physiological basis, sex differences in mutation rates may have important evolutionary consequences that warrant further exploration. Further data on the taxonomic distribution of sex-biased mutation would be of great interest, particularly in groups such as insects that vary in the mode of genetic sex determination.

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