

SEX: DIFFERENCES IN MUTATION, RECOMBINATION, SELECTION, GENE FLOW, AND GENETIC DRIFT

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In many instances, there are large sex differences in mutation rates, recombination rates, selection, rates of gene flow, and genetic drift. Mutation rates are often higher in males, a difference that has been estimated both directly and indirectly. The higher male mutation rate appears related to the larger number of cell divisions in male lineages but mutation rates also appear gene- and organism-specific. When there is recombination in only one sex, it is always the homogametic sex. When there is recombination in both sexes, females often have higher recombination but there are many exceptions. There are a number of hypotheses to explain the sex differences in recombination. Sex-specific differences in selection may result in stable polymorphisms or for sex chromosomes, faster evolutionary change. In addition, sex-dependent selection may result in antagonistic pleiotropy or sexually antagonistic genes. There are many examples of sex-specific differences in gene flow (dispersal) and a number of adaptive explanations for these differences. The overall effective population size (genetic drift) is dominated by the lower sex-specific effective population size. The mean of the mutation, recombination, and gene flow rates over the two sexes can be used in a population genetics context unless there are sex-specific differences in selection or genetic drift. Sex-specific differences in these evolutionary factors appear to be unrelated to each other. The evolutionary explanations for sex-specific differences for each factor are multifaceted and, in addition, explanations may include chance, nonadaptive differences, or mechanistic, nonevolutionary factors.

KEY WORDS: Effective population size, human diseases, mtDNA, X chromosome, Y chromosome.

Many studies have often shown strikingly large differences between the two sexes in factors determining evolutionary change and genetic variation, that is, mutation, recombination, selection, gene flow, and genetic drift. What is the basis for these differences? Are these differences correlated with sex-specific traits or the result of sex-specific adaptive differences? General population genetic models assume that the two sexes are identical in the principal factors that influence evolution. What is the impact of sex-dependent differences in these evolutionary factors on evolutionary change and genetic variation?

Most genes are on autosomes so a fundamental question is whether these sex differences have a specific impact on evolutionary changes and genetic variation for autosomal genes. The

general answer is that the arithmetic mean of the mutation, recombination, and gene flow rates over sexes is what is important for autosomal genes and differences between the sexes only appear to be important if other evolutionary factors are also significant. For selection and genetic drift, the effects over sexes are not linear and the effect in one sex may dominant the overall impact.

However, sex differences may have a special impact on genes on sex chromosomes because they spend unequal amounts of time in the two sexes. More specifically, are there differential sex-specific impacts on Y-linked genes that are always in males, Z-linked genes (ZZ males and ZW females, as in birds and Lepidoptera) that are in males two-thirds of the time, autosomes that are in males half of the time, X-linked genes (XY males and XX

females, as in mammals) and all genes in haplo-diploid organisms that are in males one-third of the time, and W-linked genes that are always in females? Data from genes on sex chromosomes may give insight into the adaptive bases for sex differences in evolutionary factors. In addition, are there any sex-specific effects on genes on organellar DNA, which is generally maternally inherited and therefore only transmitted from females (mitochondrial DNA, or mtDNA, in most organisms and chloroplast DNA, or cpDNA), although mtDNA is paternally inherited in conifers and some shellfish.

In this perspective, I will first examine sex differences in the two evolutionary factors that are part of genetic systems, mutation and recombination, and then three other evolutionary factors: selection, gene flow, and genetic drift. I will not discuss abnormal segregation (meiotic drive) (Pardo-Manual de Villena and Sapienza 2001) or genetic imprinting (Anderson and Spencer 1999; Morison et al. 2005), which are also generally sex specific for particular genes. For mutation and recombination, I will examine the evidence for sex-specific differences (and how the differences are estimated for mutation), the proposed mechanisms for differences, the proposed adaptive causes for differences, and the population genetic implications for the differences. For selection, gene flow, and genetic drift, I will concentrate on the population genetic implications for the differences.

Although there is great interest in sex differences in each of these factors, an overall perspective of these surprising findings has not been published. It is my hope to provide a general introduction and framework for future evolutionary studies on sex-dependent differences in these factors and to help evolutionary biologists integrate new data from highly informative molecular markers into an appropriate evolutionary structure. Further, I will attempt to provide an overall perspective of the importance of these different findings and examine what similarities and differences there are between them.

When considering adaptive explanations for sex differences in these factors, a fitness advantage for particular values is assumed. For sex differences in selection, this can be viewed as a direct effect. For sex differences in gene flow, say higher rates in one sex than the other, this can be nearly a direct effect if differential gene flow results in the sexes residing where they have higher fitnesses. On the other hand, mutation and recombination are considered part of the “genetic system” (Wright 1955), and although these are under genetic control (as well as influenced environmentally and varying stochastically), selection acting on these factors is indirect. As a result, this indirect or secondary selection on modifier loci that result in a change in fitness by changing sex-dependent mutation and recombination rates may be much slower and smaller in magnitude than the direct selective effects for sex-dependent selection and gene flow.

Sex differences observed for selection are generally thought to impact specific genes and perhaps the genetic region around them. On the other hand, sex differences in gene flow and genetic drift are generally thought to impact all genes equally. Sex differences in mutation or recombination are also generally thought to impact all genes but mutation and recombination rates may vary for specific genes or chromosomal regions as well as with sex. This suggests that modifier genes influencing either mutation or recombination are not always general but influence some genes or regions more than others.

Sex Differences in the Genetic System: Mutation and Recombination

MUTATION

Haldane (1935) provided the first estimation of mutation rate in humans for the common recessive bleeding disorder, X-linked hemophilia, and subsequently (Haldane 1947) estimated separately the male and female mutation rates for this disease. He concluded, “the mutation rate is much higher, and possible ten times higher, in male than in female X-chromosomes” (Haldane 1947). Subsequent estimates of a higher mutation rate in males from molecular genetic data led Miyata et al. (1987) to suggest that evolution is “male-driven.” Additional studies have generally confirmed that mutation rates are often higher in males than in females although sex differences in mutation rates appear to vary for both for different organisms and different genes.

Estimation

INDIRECT METHOD

Haldane (1947) developed an ingenious, indirect approach, assuming mutation–selection equilibrium, for estimation of the male and female mutation rates for hemophilia. He observed that males with hemophilia were much more likely to come from heterozygous mothers carrying the hemophilia allele than from homozygous, nonmutant mothers. This is consistent with the hypothesis that the mutation generally occurred in a previous generation in a male, who then passed the mutant X-chromosome to a daughter and this heterozygous female then would subsequently have a son with hemophilia. Conversely, if the mutation originally occurred in gametes from a female, then she would be homozygous nonmutant.

Haldane (1947) assumed that the proportion of affected offspring from homozygous, nonmutant mothers (m) would depend upon the male/female ratio of mutation rates (now given as $\alpha = u_m/u_f$ where u_m and u_f indicate the male and female mutation rates). He showed that

$$\alpha = \frac{s}{m} - 2, \quad (1)$$

where s is the selection coefficient against males with hemophilia. From the data available, he estimated that there was strong selection against individuals with hemophilia, $s = 0.714$, and that few mothers of hemophiliac sons were homozygous nonmutant, $m = 0.041$. Using these values, his estimate of $\alpha = 15.4$ suggested that the mutation rate was much higher in males than females. Subsequently, Rosendaal et al. (1990) provided an approach that did not require an assumption of equilibrium and found that $\alpha = 3.1$ in a meta-analysis of six hemophilia A studies. Oldenburg et al. (1993) used the approaches of both Haldane (1947) and Rosendaal et al. (1990), and a direct approach (see below), and found that all approaches showed a higher hemophilia mutation rate for males than for females.

DIRECT METHOD

With the advent of detailed molecular genetic techniques, a direct approach is possible in which new mutants are identified using DNA sequence data from the parents and mutant offspring as either paternal or maternal in origin. Li et al. (2002) summarized the direct estimates of α as 10.7 (204 paternal and 19 maternal mutations) for 11 dominant human diseases from eight different genes (Table 1). Strikingly, all the 40 achondroplasia and the 57 Apert syndrome mutants examined, both autosomal dominant diseases at related genes, were paternal. On the other hand, for two other autosomal dominant diseases, α is near unity. A search of recent literature found parental identification of mutations for six other autosomal diseases caused by five different genes (Table 1). Of the 103 mutations identified, 92 were paternal and 11 were maternal, with $\alpha = 8.4$. Including the data from the Li et al. (2002) survey, the overall $\alpha = 9.9$ using direct parental identification of the mutants.

EVOLUTIONARY METHOD

Miyata et al. (1987) suggested another indirect approach, now generally called the evolutionary method, to estimate the ratio

of the male and female mutation rates from nucleotide sequence data by comparing sex chromosomes and autosomes. This widely adopted approach generally uses gene substitution rates on homologous DNA sequences on different chromosomes and assumes that these sequences are evolving neutrally so that observed rates of substitution are equal to the mutation rates. It is also assumed that the substitutions rates for sequences on different chromosomes are a function of the proportion of time spent in males and females. For example, X chromosomes, autosomes (A), and Y chromosomes are in males, one-third, half, and all of the time, respectively.

Assuming neutrality for genes on the Y chromosome, the rate of substitution $Y = u_m$, is the mutation rate in males. For genes on the X chromosome, the rate of substitution $X = (2u_f + u_m)/3$ because these genes are in males only one-third of the time. Assuming that $u_m = \alpha u_f$, then the ratio of the observed rates of substitution for genes on the Y and X chromosomes is

$$\frac{Y}{X} = \frac{u_m}{\frac{1}{3}(2u_f + u_m)} = \frac{\alpha u_f}{\frac{1}{3}(2u_f + \alpha u_f)} = \frac{3\alpha}{2 + \alpha} \quad (2a)$$

and

$$\alpha_{Y/X} = \frac{2Y}{3X - Y} \quad (2b)$$

If there is no mutation in females, that is, $u_f = 0$, then $Y/X = 3$ and $\alpha_{Y/X} = \infty$, as expected.

Similarly, the ratio of Y and A substitution rates and $\alpha_{Y/A}$ are

$$\frac{Y}{A} = \frac{2\alpha}{1 + \alpha} \quad \text{and} \quad \alpha_{Y/A} = \frac{Y}{2A - Y} \quad (3)$$

and the ratio of X and A substitution rates and $\alpha_{X/A}$ are

$$\frac{X}{A} = \frac{2(2 + \alpha)}{3(1 + \alpha)} \quad \text{and} \quad \alpha_{X/A} = \frac{4A - 3X}{3X - 2A} \quad (4)$$

Table 1. Human diseases in which the number of paternal or maternal mutations has been determined directly using molecular data, and the resulting estimate of α (male/female ratio of mutations) (RTK genes indicates receptor tyrosine kinase gene family which includes genes *FGFR2*, *FGFR3*, and *RET*).

Disease	Gene	Paternal	Maternal	α	Source
Alexander disease	<i>GFAP</i>	24	4	6	Li et al. (2006)
Costello syndrome	<i>HRAS</i>	23	2	11.5	Sol-Church et al. (2006), Zampino et al. (2007)
Muenke-type craniosynostosis	<i>FGFR3</i> *	10	0	∞	Rannan-Eliya et al. (2004)
Noonan syndrome	<i>PTPN11</i>	14	0	∞	Tartaglia et al. (2004)
Townes-Brocks syndrome	<i>SALL1</i>	14	2	7	Böhm et al. (2006)
Treacher Collins syndrome	<i>TCOF1</i>	7	3	2.33	Splendore et al. (2003)
Subtotal		92	11	8.4	
11 diseases	8 genes	204	19	10.7	Li et al. (2002)
Total		296	30	9.9	
Total (without RTK genes)	10 genes	132	27	4.9	

*Mutations in *FGFR3* also cause achondroplasia.

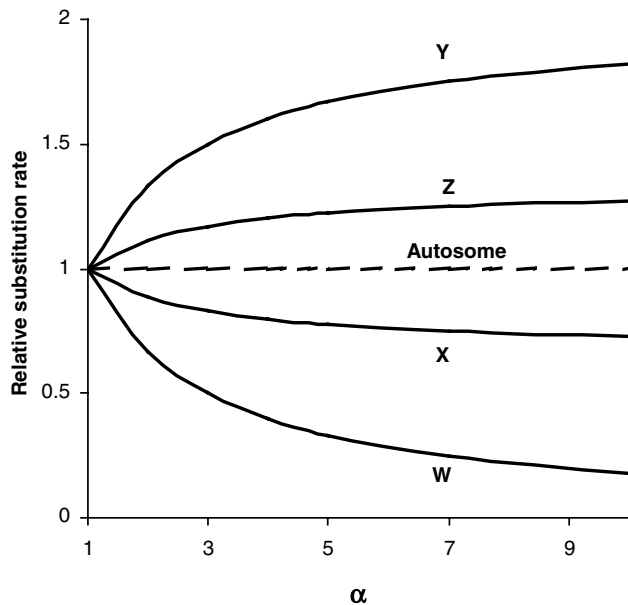


Figure 1. The rate of substitution for genes on the X, Y, W, and Z chromosomes, relative to that for autosomal genes, for different values of α , the ratio of the male to female mutation rate.

To illustrate these relationships, Figure 1 gives the substitution rate for genes on the Y and X chromosomes, relative to that for autosomal genes, as a function of α . As α increases, the relative substitution rate of genes on the Y chromosome increases asymptotically to 2 and the relative substitution rate of genes on the X decreases asymptotically to two-thirds.

Recent estimates of α using this approach are around 4 in primates (Goetting-Minesky and Makova 2006), significantly above 1 but somewhat lower than earlier estimates in primates and that obtained from direct estimation for human diseases above. However, Patterson et al. (2006) estimated that the primate α is 1.9, after correcting for the low human–chimpanzee divergence on the X chromosome. Estimates of α in cats, sheep, and horses are also around 4 (Goetting-Minesky and Makova 2006) and estimates in mice and rats are around 2 (Makova et al. 2004; Sandstedt and Tucker 2005). Using divergence estimates from X and A from *Drosophila melanogaster* by Bauer and Aquadro (1997), $\alpha_{X/A} = 0.82$ for divergence for nonhomologous genes at silent sites and only 0.15 for divergence in introns.

An independent test of the male-biased mutation hypothesis is the examination of the sex differences in substitution rates in birds where males are ZZ and females ZW (Miyata et al. 1987). As a result, Z chromosomes are in males two-thirds of the time and W chromosomes are found only in females. Using the same approach as above, and assuming that Z and W are the substitutions rates for genes on the Z and W chromosomes, then

$$\alpha_{Z/W} = \frac{3Z - W}{2W}. \quad (5)$$

Figure 1 also gives the substitution rates for genes on Z and W chromosomes relative to that on autosomes for different levels of α . The first estimates of α for Z–W sequences were 6.5 (Ellegren and Fridolfsson 1997) and 4 (Kahn and Quinn 1999) but more recent and comprehensive estimates are around 2, although there is significant heterogeneity in these estimates in different species (Axelsson et al. 2004) and different chromosomal regions (Berlin et al. 2006).

MECHANISM

Haldane (1947) suggested the following general mechanism for the sex differences in mutation rate: “The primordial oocytes are mostly if not all formed at birth, whereas spermatogonia go on dividing throughout the sexual life of a male. So if mutation is due to faulty copying of genes at a nuclear division, we might expect it to be commoner in males than females.” Previously, Weinberg (1912) observed that children with achondroplasia had normal, but older, parents and suggested that mutation was the cause. Subsequently, Penrose (1955) demonstrated that this increase in new mutations appeared to be a function of age of the father, not of the mother.

The germ line in human males has many more cell divisions, or DNA replications, than that in females. In the production of mature ovum in females there are 23 cell divisions, all completed before birth, so there is no increase with postnatal age (Crow 2000, 2006). In the germ line of males there are about 30 cell divisions before puberty and then one about every 23 days so that there are about 150, 380, and 610 replications for 20-, 30-, and 40-year olds (Crow 2000, 2006). As a result, the ratio of cell divisions (c) for 20-, 30-, and 40-year-old males to females are about 6.5, 16.5, and 26.5, respectively. If human male mutation is replication dependent and the average age at reproduction is around 20, then α should be similar to c in value, around 6 in humans (Chang et al. 1994) and there should be an increase in mutation rate with male age.

Kahn and Quinn (1999) estimated that in birds (Japanese quail and chickens), c is about 4.5 and Chang et al. (1994) estimated that in rodents the male germ line has about twice as many replications as the female germline. Bauer and Aquadro (1997) calculated that the male-to-female ratio in the number of cell divisions in *D. melanogaster* was around 1. Overall, the male-mutation bias discussed above is higher for organisms with longer generations, presumably reflecting the higher number of male germline cell divisions in organisms with longer generations (Goetting-Minesky and Makova 2006). That is, α is largest for primates, somewhat lower for birds, cats, sheep, and horses, lower yet for mice and rats, and not greater than unity for *Drosophila*. In addition, there is evidence that plants have a higher mutation rate at homologous genes on Y than on X chromosomes (Filatov and Charlesworth 2002) and on paternally than on maternally

inherited organellar genes (Whittle and Johnston 2002), an observation not inconsistent with the larger number of cell divisions in pollen than in ovule production (Klekowski 1988).

However, it appears that replication-independent factors influencing mutation rate, such as genomic region, nucleotide composition, and even life history (Bartosch-Härlid et al. 2003), may be as, or more, important than replication-dependent factors (Ellegren 2007). For example, Taylor et al. (2006) showed that α estimates depend importantly upon the type of mutation site (CpG or not), the type of chromosomal comparison, and the amount of ancestral polymorphism. The mechanism of mutation may be important as to whether mutation is replication independent. For example, some mutations do not occur during cell division (CpG mutations are due to deamination of cytosine via UV radiation) and likely occur more or less equally in males and females. Further, a recent detailed examination in sperm of male age on mutation rates showed an effect for some but not for other disorders (Wyrobek et al. 2006; see also Tiemann-Boege et al. 2002; Brohede et al. 2004), not strongly consistent with the male replication-dependent mutation model. For example, examination of mutation rates in sperm for the gene causing achondroplasia from males of different ages showed only a small increase in mutation rate with age, not nearly enough to explain the observed increase in the disease with paternal age (Tiemann-Boege et al. 2002).

Crow (2006) reported some exceptions to male-mutation bias in two human diseases, Duchenne muscular dystrophy and neurofibromatosis, and suggested that base substitutions appear male biased whereas small deletions are not. Similarly, there appears to be heterogeneity in male bias for hemophilia A mutations with a high male bias for point and inversion mutations and a female bias for deletion mutations (Oldenburg et al. 2004). However, a whole-genome analysis of small indels in rodents found a male bias similar to that for nucleotide substitutions (Makova et al. 2004). In addition, there is a strong female bias for full fragile X mutations in humans (Fu et al. 1991) and all 33 mutants observed at a microsatellite locus in a sea turtle were maternal (Hoekert et al. 2002).

Mutation for some of the diseases with strong male bias, such as Achondroplasia and Apert syndromes, result from mutations at “hot spot” sites at specific codons within the gene (Crow 2006). In addition, the high mutation at gene *FGFR2*, which causes Apert syndrome, appears to be the result of a selective advantage of the mutant protein in spermatogonial cells (Goriely et al. 2003; Goriely et al. 2005; Crow 2006; Qin et al. 2007). If the members of the receptor tyrosine kinase gene family, which includes the *FGFR2* gene, are excluded from the data in Table 1, then the α for the 10 remaining genes is greatly reduced to 4.9. Li et al. (2002) suggested that the direct mutation rate data are not be indicative of overall mutation rates and α because a number of the observed

mutations appear to be at mutational hot spots whereas estimates from the evolutionary method are the result of a large number of sites and the cumulative effect over a long time.

There has also been the suggestion that recombination may be mutagenic, that is, mutations are more likely to occur in regions of recombination. Supporting this hypothesis, Lercher and Hurst (2002) found an association of synonymous divergence between human and mouse genes and recombination rate. Subsequently, Filatov and Gerrard (2003) observed that in the pseudoautosomal region (PAR) of the human sex chromosomes, which has very high recombination, there was a high substitution rate. On the other hand, Huang et al. (2004) found only a weak effect of recombination in the PAR on substitution rate in mice. Hellman et al. (2003) and Spencer et al. (2006) examined in detail the association of recombination and mutation in humans and discuss the implications of their findings. If this hypothesis were generally true because human recombination rate is about 60% higher in females (see below), then one would expect the mutation rate to be higher in females, not males, as observed. As a result, it appears that a large amount of mutation is not related to recombinational events.

EVOLUTIONARY CAUSE

There has been an interest in the evolution of mutation rates since Sturtevant (1937) asked “why does the mutation rate not evolve to zero?” Kimura (1967) proposed that there is evolutionary adjustment of mutation rates that maximizes fitness, Kondrashov (1995) suggested selective reduction of mutation rates is balanced by the cost of fidelity, and Drake et al. (1998) summarized the evolutionary factors that influence mutation rates. A general theoretical perspective is that level of mutation is a balance between deleterious mutations reducing fitness, advantageous mutations increasing fitness, and cost in fitness from mutation repair mechanisms to reduce the mutation rate (Sniegowski et al. 2000). The relative importance of these factors may vary but because most mutations are generally less fit than the present wild type, selection generally should act to reduce the mutation rate by improving the repair mechanisms. However, the strength of indirect selection changing the mutation rate, either increasing it or decreasing it, is quite low and is on the order of the change in the mutation rate caused by a modifier locus (Sniegowski et al. 2000).

Using the context above, sex differences could be the evolutionary result of selection for a more efficient lowering of the detrimental mutation rate in females, a retention of a higher advantageous mutation rate in males, less cost for lowering the mutation rate in females, or a combination of these factors. One evolutionary hypothesis for sex differences in mutation rates is that there may be different selective optima in the two sexes balancing the deleterious mutation rate and the cost of efficient repair and replication (Ellegren 2007). More specifically, if we assume that the

major impact of selection on mutation rate is to minimize the mutation rate per replication as much as possible to reduce rate of deleterious mutation, then any sex differences observed in mutation rate may be related to the different number of replications in the two sexes. In other words, if the major impact of selection is to reduce mutation rate as much as possible, it has been generally more successful in females, either because of more male replications or because repair mechanisms are more efficient in females than males for some reason. Consistent with this, Crow (2000) suggests that an increase in mutation rate at later reproductive ages is not surprising. His reasoning is that until recent times few men would live into their forties so there would have been little selection pressure to reduce the detrimental effects of mutations from older men. Or, the sex differences in mutation rate may not have a strong evolutionary basis and are primarily the result of sex differences in gametogenesis.

POPULATION GENETIC IMPLICATIONS

How can sex differences in mutation rate be incorporated into population genetics? The rate of mutation for an autosomal gene can be given as the arithmetic average of the mutation rate in males and females or

$$\bar{u} = (u_m + u_f)/2 = u_f(1 + \alpha)/2 \tag{6a}$$

(Table 2). In other words, a higher male mutation rate increases the average mutation rate for an autosomal gene (and consequently also increases the rate of gene substitution). Or, selection for a reduction in mutation rate in females can only decrease the mean mutation rate so much if the male mutation rate is high. Of course, autosomal mutations in males are equally likely to be in males and females in the next generation so that the sex origin of the mutation is quickly lost.

For the sex chromosomes, the mean mutation rate is a function of the proportion of time the chromosome spends in each sex as discussed above. For example, for X chromosomes,

$$\bar{u} = (u_m + 2u_f)/3 = u_f(2 + \alpha)/3. \tag{6b}$$

Therefore, the mean absolute mutation rate and substitution rate (assuming neutrality) increase as the male mutation rate increases.

But, relative to that for genes on autosomes, the mean mutation rate and rate of substitution on X chromosomes decline as α increases (Fig. 1).

In addition, a higher male mutation rate should differentially influence the amount of genetic variation for neutral autosomal and X-linked loci. Hedrick and Parker (1997) compared the amount of variation in humans for 5048 microsatellite loci on autosomes and 216 microsatellite loci on the X chromosome. The effective population size for an X-chromosome gene is expected to be 0.75 that of an autosomal gene (see below). They found that the observed amount of variation for the X-chromosome loci, relative to that for autosomal genes, was 0.708 assuming a stepwise mutation model and 0.796 assuming an infinite allele model, bracketing the expected 0.75 value predicted under neutrality, a conclusion inconsistent with male-biased estimates of mutation rates. Direct estimates of human microsatellite mutation rates have shown either male bias (Weber and Wong 1993) or no male bias (Huang et al. 2002). On the other hand, The SNP (single nucleotide polymorphism) Consortium (Sachidanandam et al. 2001) report of 1.42 million SNPs found that X-linked SNPs had diversity of only 0.59 that of autosomal SNPs. Assuming that $\alpha = 5$, then the X/A ratio should be 0.58, close to the observation for SNPs.

Kirkpatrick and Hall (2004) investigated the impact of sex differences in the mutation rate when there is selection. When there is advantageous selection and additivity, the relative substitution rates for different sex chromosomes is equal to the sex differences in mutation rate, as given in Figure 1. However, when there are different levels of dominance, the relative rates of substitution may change. For example, when α is large, an advantageous Z-linked mutant has a higher rate of substitution than an autosomal gene over most dominance levels.

Recombination

EVIDENCE AND ESTIMATION

The level of recombination in the genomes of different organisms varies greatly with sex. As extremes, early last century it was discovered that in *Drosophila* there is no recombination in males and in *Bombyx* (bumblebees) there is no recombination in females (Haldane 1922). Species with recombination in only one sex are termed achiasmate species, and in a large survey, Bell (1982)

Table 2. The average over both sexes of mutation, recombination, and gene flow rates and overall effective population size for genes on autosomes, X chromosomes, Y chromosomes, and mtDNA.

	Autosome	X chromosome	Y chromosome	mtDNA
Mutation (\bar{u})	$\frac{1}{2}(u_m + u_f)$	$\frac{1}{3}(2u_f + u_m)$	u_m	u_f
Recombination (\bar{c})	$\frac{1}{2}(c_f + c_m)$	$\frac{2}{3}c_f$	0	0
Gene flow (\bar{m})	$\frac{1}{2}(m_f + m_m)$	$\frac{1}{3}(2m_f + m_m)$	m_m	m_f
Effective population size (N_e)	$\frac{4N_{ef}N_{em}}{N_{ef} + N_{em}}$	$\frac{9N_{ef}N_{em}}{2N_{ef} + 4N_{em}}$	$\frac{1}{2}N_{em}$	$\frac{1}{2}N_{ef}$

estimated that achiasmy has evolved independently approximately 30 times.

For species with recombination in both sexes, heterochiasmate species, there is a great range in the ratio of female to male recombination (for extensive species lists, see Burt et al. 1991; Lenormand and Dutheil 2005). The highest value reported to date in any vertebrate is in Atlantic salmon where the rate of recombination in females is 8.26 that in males (Moen et al. 2004) whereas Gilbey et al. (2004) estimated a ratio of 3.92 in Atlantic salmon and Gharbi et al. (2006) estimated a ratio on 6.4 in related brown trout. The level of female to male recombination ratio in *Ara-bidopsis thaliana* is 1.68 (Drouaud et al. 2007), in humans is 1.65 for autosomal genes (Kong et al. 2002; Matise et al. 2003), and in mice is 1.26 for autosomal genes (Shifman et al. 2006). On the other hand, the lowest female to male recombination ratio reported to date is in the Japanese flounder where the ratio is only 0.14 (Coimbra et al. 2003).

In addition, the pattern of recombination varies with sex, with human males having higher recombination at telomeric regions and females having higher recombination near the centromere (Kong et al. 2002). By manipulating the sex chromosome constitution of experimental mice, Lynn et al. (2005) showed that it appears that “sex-specific differences in the pairing and synapsis of seven homologs set up spermatocytes and oocytes to have different exchange patterns” and that the sex-chromosome constitution does not determine sex-specific recombination rates and patterns. Further, the correlation between female and male recombination rates in mice across the genome is weak (Shifman et al. 2006), supporting the importance of sex-specific differences in recombination.

Sex-specific levels of recombination are generally determined from a cross, or crosses, of known female and male parental genotypes so that recombination between given markers for the two sexes can be measured in the progeny. The overall sex-specific levels of recombination are estimated from genetics maps thus generated from males and females or in some cases, from cytological indicators, such as chiasmata, or indicators of chiasmata (Calderon and Pigozzi 2006), in cells from the two sexes. Burt et al. (1991) stated that for organisms with both estimates of chiasmata number and genetic maps, there was a high correlation between the two datasets. Recombination in humans at a fine scale can be directly determined in males by examining large numbers of sperm from given individuals whereas comparable studies of female recombination are not possible (Arnheim et al. 2003).

EVOLUTIONARY CAUSE

Is there an evolutionary explanation for the diversity of sex differences in recombination over species? Recognizing that the sexes that had no recombination in *Drosophila* (males) and *Bombyx*

(females) were both heterogametic and other related observations, Haldane (1922) hypothesized that pleiotropic selection against recombination between different sex chromosomes would result in lower recombination rate for autosomes in the heterogametic sex. Quoting Haldane (1922), “If on the other hand a number of factors determine it (sex), it is essential that they should be linked. . . . As soon as another factor becomes necessary, complete linkage between the two must appear in the heterozygous sex, and the same mechanism which prevents them from crossing over may be expected to hinder or prevent crossing over of all factors in that sex.”

Subsequently, Huxley (1928) gave the same evolutionary explanation for his observations in the amphipod *Grammarus*. This observation, that when one sex does not have recombination, it is the heterogametic sex, is now generally known as the Haldane–Huxley rule, has been found for all achiasmate species examined (Lenormand and Dutheil 2005). [Note that this is different from Haldane’s rule, which is, “When if the F_1 of two different animal races one sex is absent, rare or sterile, that sex is the heterozygous sex” (Haldane 1922).] All the independent evolutionary events to achiasmy reported by Bell (1982) and Burt et al. (1991) were in the heterogametic sex (however, see Lenormand 2003). Nei (1969) demonstrated theoretically that sex differences in recombination could evolve by reducing recombination between sex-determining genes on the sex chromosomes. However, Lenormand and Dutheil (2005) have recently offered an appealing alternative explanation for the Haldane–Huxley rule. In brief, they suggest that in organisms selected for reduced recombination that the presence of no recombination only in the heterogametic sex reflects selection to maintain recombination on the X or Z chromosomes in the homogametic sex.

What are the potential evolutionary reasons for sex differences in recombination rates in species with recombination in both sexes? Table 3 lists and describes the four main evolutionary hypotheses that have been suggested and summarizes some comments about them. The pleiotropy hypothesis does not explain a number of observations so it cannot be the only explanation for sex differences in recombination for heterochiasmate species. For example, the relative levels of recombination in the two sexes do not appear to be completely consistent with the sex heterogamy (Lenormand and Dutheil 2005).

In the Japanese flounder, which has the lowest female to male ratio known, the female is the heterogametic sex, and in many mammals, including humans, the male is the heterogametic sex and has lower recombination, but there are a number of exceptions. For example, the female to male recombination ratio is 0.79 in domestic sheep (Crawford et al. 1995), and in the marsupial, short-tailed opossum, where the male is the heterogametic sex, the female to male recombination rate is 0.50 (Samollow et al. 2004). However, in the major histocompatibility complex region

Table 3. The evolutionary hypotheses proposed to account for sex differences in recombination in species with recombination in both sexes.

	Hypothesis	Comments
Pleiotropy (Haldane 1922)	Selection against recombination between different sex chromosomes results in lower recombination rates for autosomes in the heterogametic sex	Not consistent with data from some heterogametic species, from species without sex chromosomes, or different regions of the genome (Lenormand 2005)
Sexual selection (Trivers 1988)	Selection lowering recombination is stronger in males than females because sexual selection in males results in stronger selection to preserve favorable combinations	Not consistent with data from species with higher male recombination, no quantitative analysis of correlation of sex-specific levels of sexual selection and recombination, not supported by test of species with different levels of sexual dimorphism (Burt et al. 1991; Lorch 2005)
Neutral (Burt et al. 1991)	Sex differences in recombination are not determined by differential selection, only the mean value of recombination is under selection	Female and male recombination values are correlated although this may be predicted under a modified neutral hypothesis (Burt et al. 1991)
Haploid selection (Lenormand 2003)	Sex with more intense haploid selection should have less recombination	Recombination levels consistent with opportunity for male and female haploid selection in plants but in animals, no haploid selection in females and little in males (Lenormand and Dutheil 2005)

for the short-tailed opossum, the two sexes have similar rates of recombination (Gouin et al. 2006), suggesting that other factors are important in determining local recombination rates. There is evidence from cytological and linkage map analysis that there is no sex-dependent recombination in four species of birds (pigeons, Japanese quail, chickens, and zebra finch) where the female is heterogametic (Calderon and Pigozzi 2006). The only report showing sex differences in a passerine (great reed warbler) (Hansson et al. 2005) was a 2.2-fold higher recombination in the females than males (inconsistent with the Haldane–Huxley rule).

In addition, some hermaphroditic species, without sex chromosomes or even sex-determining genes, have significant heterochiasmy (Lenormand and Dutheil 2005). A recent linkage map in the saltwater crocodile, which does not have sex chromosomes and where sex is determined by temperature, found that there is higher recombination in females than males (Isberg et al. 2006). Finally, there are examples of significant variation in sex-dependent recombination for different autosomes within the same species (Lenormand and Dutheil 2005). As a result, it has been suggested that the evolutionary factors influencing the presence of achiasmy and sex differences in the quantitative level of recombination are different (Burt et al. 1991; Lenormand and Dutheil 2005).

Trivers (1988) provided the first main alternative hypothesis, suggesting that recombination should be lower in males because they undergo stronger sexual selection. As a result, decreased recombination would permit these successful males to

pass on their successful unrecombined gametes. However, females of some species have lower recombination than males; Trivers (1988) countered that in these species there may be more sexual selection on females. To evaluate the sexual selection hypothesis, Burt et al. (1991) examined three groups of species with different levels of sexual dimorphism (as a surrogate for different levels of sexual selection) for sex differences in recombination and found no effect. Further, Burt et al. (1991) suggested a contrary model in which the sex with more sexual selection, that is, more variance in reproductive success and more genetic drift, should have more recombination. Finally, Lenormand (2003) demonstrated theoretically that sex-specific diploid selection was unsuccessful in causing sex differences in recombination.

Burt et al. (1991) suggested that sex differences in recombination may not be under selection but only the mean value of recombination is under selection. There is a large body of theoretical research investigating the situations in which lower or higher levels of recombination are advantageous (Otto and Lenormand 2002; Coop and Przeworski 2007) but except for the study by Lenormand (2003) on haploid selection there does not appear to be any theoretical evolutionary explanation for sex differences in recombination. Burt et al. (1991) suggested that recombination rate differences between the sexes within a species are “neutral” and should be uncorrelated. Their examination of published values suggested a strong correlation and they therefore rejected the neutral hypothesis in its simplest form. However, as they suggested, a modified neutral hypothesis may be reasonable

in which there are no selective effects on sex differences in recombination rates for smaller differences in recombination rates and costs of recombination only occur with much higher (or lower) recombination. If selection is on the mean rate of recombination and if one sex has low recombination, then selection should act to increase recombination in the other sex as compensation (Burt et al. 1991). As an illustration of this, Burt et al. (1991) summarized data that indicated the X chromosome in female mice has a higher than expected recombination rate (the X chromosome in male mice has no recombination). However, a recent detailed study (Shifman et al. 2006) found that the X chromosome in mice had a lower, not higher, recombination rate than the genomic average, even when standardized by two-thirds as suggested by Butlin (2005).

Lenormand (2003) showed theoretically that sex differences in haploid selection could result in sex differences in recombination (sex differences in recombination could not easily be explained by sex differences in diploid selection). Assuming that there is epistasis between genes influencing fitness, he showed that the sex with the more intense haploid selection should have a lower recombination rate. This lower recombination results in a greater fitness because it minimizes the recombinational load. Lenormand and Dutheil (2005) examined male and female recombination rates in a number of species to evaluate the haploid selection hypothesis. In plants, they found that sex differences in recombination were correlated with the opportunity for haploid selection in males and females. For example, in pines where there is intense haploid selection in females, there is lower female than male recombination. On the other hand in animals, there is generally no female haploid phase because meiosis is only complete at fertilization, and therefore no opportunity for female haploid selection. In male animals, only a few genes are expressed and potentially selected in the haploid phase, however, this is consistent with the hypothesis that there would be lower recombination in males. However, for some animal species the female recombination rate is lower than that in males.

Overall, the relative importance of these four evolutionary hypotheses on sex differences in recombination is difficult to judge and maybe more than one is significant in a given species. As discussed for mutation, it is possible that past selection acting to reduce or increase the mean recombination rate has been more effective in one sex than the other for some reason with a consequent current sex difference in recombination rates. In addition, mechanistic, physiological, or other factors may differentially constrain or influence the potential range of recombination in the two sexes. For example, the high female to male recombination in salmonids is thought to be related to their autotetraploid ancestry and that they have not yet established full disomy, with multivalent formation restricted to males (Allendorf and Danzmann 1997). Or, one sex may have more genetic variation for recombi-

nation so that it would respond more to selection for a change in recombination.

POPULATION GENETIC IMPLICATIONS

To accommodate recombination differences in the two sexes, the mean recombination rate between two autosomal loci \bar{c} can be given as

$$\bar{c} = (c_f + c_m)/2 \quad (7a)$$

where c_f and c_m are the recombination values in females and males, respectively (Table 2). As with mutation, a higher or lower recombination rate in one of the sexes is limited in changing the mean recombination rate by the recombination rate in the other sex. Also, the sex origin of a recombination event at an autosomal gene is quickly lost in future generations.

For two loci on an X chromosome,

$$\bar{c} = 2c_f/3 \quad (7b)$$

because recombination on X chromosomes occurs only in females and X chromosomes are in females two-thirds of the time (for Z chromosome genes, the rate of recombination is $2c_m/3$). For the region of the Y chromosome that is nonhomologous to the X chromosome, known as the nonrecombining region (NRY) in humans, there is no recombination. For mtDNA, there is generally no recombination although there have been some reports of very low levels of recombination.

For neutral loci in a large population, the major impact of the recombination rate is on the approach to linkage equilibrium. In organisms with recombination in only one sex, the approach to linkage equilibrium is half as fast as in organisms with recombination in both sexes. For X-linked genes and genes in haplo-diploid organisms, in which there is no recombination in males, the rate of decay is generally two-thirds that for autosomal genes but is often more complicated because the sexes may differ in gamete frequencies (Bennett and Oertel 1965).

Sex Differences in Evolutionary Factors: Selection, Gene Flow, and Genetic Drift

GENERAL EFFECTS

Differential selection, gene flow, or genetic drift in the two sexes can make allele frequencies in males and females substantially different. Sex differences in selection generally influence allele frequencies at particular loci, and the regions near them, whereas sex differences due to genetic drift or gene flow may influence allele frequencies throughout the genome. The sex difference in

allele frequencies violates one of the assumptions of the Hardy–Weinberg principle that the parents of both sexes have the same allele (or genotype) frequencies. To consider this, assume that at an autosomal locus p_f and p_m represent the frequencies of A_1 in females and males, respectively, q_f and q_m the analogous frequencies of A_2 , the overall (mean) frequencies of the two alleles is $\bar{p} = 1/2(p_f + p_m)$ and $\bar{q} = 1/2(q_f + q_m)$, and P , H , and Q are the frequencies of genotypes A_1A_1 , A_1A_2 , and A_2A_2 , respectively. When the parental allele frequencies differ between the sexes, in the progeny there will be an excess of heterozygotes and a deficiency of homozygotes over the Hardy–Weinberg proportions. The amount of deviation for heterozygotes from Hardy–Weinberg proportions is (Robertson 1965; Purser 1966; Brown 1979)

$$H - 2\bar{p}\bar{q} = 1/2(p_f - p_m)^2. \quad (8a)$$

For small differences in allele frequency between the two sexes, the increase in heterozygosity is minor but if the differences in allele frequency are large, then there can be a substantial effect. When there are multiple alleles and differences in allele frequencies between the sexes, the frequencies of all heterozygotes combined are elevated and those of all homozygotes combined are decreased. Similarly, sex differences in haplotype frequencies may result in an excess of heterozygous diplotypes over Hardy–Weinberg expectations. Of course, these deviations from Hardy–Weinberg proportions are only expected to last one generation without further sex-dependent perturbations in allele frequencies.

If the difference in allele frequency between the sexes is the result of genetic drift, then the term on the right side of the above equation equals pq/N_e and the equation can be solved for an estimate of effective number of parents N_e (Pudovkin et al. 1996). Luikart and Cornuet (1999) showed that the confidence intervals on this estimate were very large except when the effective number of parents were quite small so this estimate may be useful only in restricted situations.

Genes on the X chromosome in mammals and other organisms and all genes in haplo–diploid organisms have the same pattern of inheritance (the Z chromosome in birds and some insects have a complementary one). In this situation, if there is an initial difference in allele frequencies in the two sexes, then equal allele frequencies in the two sexes are achieved only over several generations and the deviation in heterozygosity from Hardy–Weinberg expectations in the XX females also disappears gradually with time. Assuming equal numbers of the two sexes, then two-thirds of the alleles are in the females and one-third is in males and the mean frequency of A_2 is $\bar{q} = 2/3 q_f + 1/3 q_m$. When the parental allele frequencies in the two sexes differ, there is also an excess over

Hardy–Weinberg proportions in the heterozygous diploid female progeny as

$$H - 2\bar{p}\bar{q} = \frac{1}{9}[(4p_f - p_m)(p_f - p_m) + (4q_f - q_m)(q_f - q_m)] \quad (8b)$$

(Hedrick 2005). This deviation may be substantial because allele frequencies for X-linked or haplo–diploid genes can easily differ in the two sexes.

The excess of heterozygotes from sex differences in allele frequencies may influence the impact of other evolutionary factors. For example, the excess of multilocus heterozygotes from differential frequencies of gametes or haplotypes in the two sexes may result in more effective recombination and a faster decay of linkage disequilibrium. In addition, such an excess of heterozygotes may result in a greater retention of genetic variation from selection favoring heterozygotes in a finite population, that is, a reduction in the effect of genetic drift.

Selection

Differential selection in males and females has long been a topic of research and discussion, starting with Darwin (1871). Here I will only discuss some aspects of this topic and give brief introductions and some references for others. The emphasis is on sexually antagonistic selection and considers in order the contexts of sexual dimorphism, antagonistic pleiotropy, and sexually antagonistic genes. For species that are sexually dimorphic, such as many birds and mammals, it is presumed that selection pressures have been significantly different enough in the two sexes to lead to differences in morphology, behavior, resistance to disease, or other phenotypic characters. Recent studies have demonstrated strong sex-dependent gene expression (Meiklejohn et al. 2003; Ranz et al. 2003; Kaiser and Ellegren 2006; Pröschel et al. 2006; Vicoso and Charlesworth 2006; Ellegren and Parsch 2007), suggesting that these genes may important in sex-dependent selection.

Often sexual dimorphism is attributed to sexual selection, that is, selective differences in mate selection resulting from male competition among mates and female choice of mates (Andersson 1994; Shuster and Wade 2003). In most of these cases, the males of many species of birds, mammals, amphibians, fish, and insects, have extreme morphological or behavioral traits that appear to have evolved because they enhance the individual's odds either of winning in male–male competition to obtain matings with females or of attracting or persuading females to mate with him. In other words, variation in male phenotypic traits is assumed to indicate differences in male genetic quality with the most extreme male individuals assumed to be those with the highest fitness.

Females may have the ability to choose mates with extreme morphological or behavioral characteristics over less extreme

males. For female preference to result in selection favoring extreme phenotypes, females must be able to perceive accurately differences in male size, shape, sound, and so on. It is generally thought that females choose mates that can provide important resources. Female choice may also reflect females choosing males with “good genes,” for example, more brightly colored males may have greater genetic resistance to parasites (Hamilton and Zuk 1982). The traits involved in male-mating success and female choice may be under strong selection in other ways (Ryan 1998). Because of higher mortality for extreme traits, the response to sexual selection may reach a limit beyond which the cost in male viability is greater than the advantage in male mating resulting in a balance between sexual selection and natural selection (Endler 1980; Heinsohn et al. 2005).

POPULATION GENETIC IMPLICATIONS

In many organisms, environmental factors may vary for individuals of the two sexes, sometimes related to aspects of sexual selection or reproduction. As a result, there are a number of examples in which the two sexes of a species may have different viability values (Selander 1966; Hedrick 1993; Butler et al. 2007). Particularly interesting is when directional selection occurs in opposite directions in the two sexes and leads to a stable polymorphism. Haldane (1962) investigated the situation of complete dominance in which the fitnesses of females were 1, 1, and 1 + *s_f*, and males were 1, 1, and 1 – *s_m* for genotypes *A₁A₁*, *A₁A₂*, and *A₂A₂* and showed that there was a stable polymorphism when

$$s_f > s_m > \frac{s_f}{1 + 2s_f} \tag{9}$$

For example, when *s_f* = 1, *A₂A₂* females have twice the fitness of the other genotypes, 1 > *s_m* > 1/3, quite a large range. However, when *s_f* is small, say *s_f* = 0.1, then 0.1 > *s_m* > 0.083, a rather small range. Further, Livingstone (1992) showed that the approach to the equilibrium frequency for this model is extremely slow.

Kidwell et al. (1977) also investigated the situation in which selection occurs in opposite directions in the two sexes when heterozygotes are intermediate, that is, 1 – *s_f*, 1 – *s_f*/2, and 1 in females and 1, 1 – *s_m*/2, and 1 – *s_m* in males. They found that there is a stable equilibrium when

$$\frac{s_m}{1 - s_m} > s_f > \frac{s_m}{1 + s_m} \tag{10a}$$

The region for this stable equilibrium is as shown between the solid lines in Figure 2 and a fairly large range of selection values will result in a stable polymorphism. However, when selection is not large, the conditions for a polymorphism become quite restrictive. For example, if *s_m* is 0.1, then *s_f* must be between 0.091 and

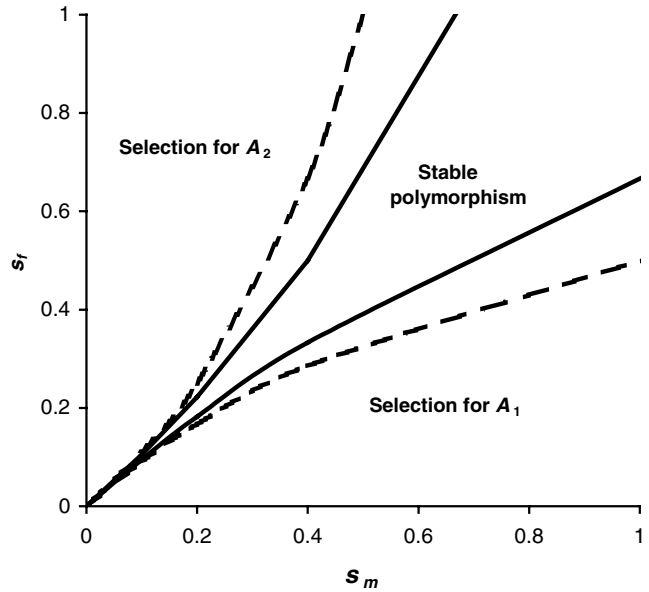


Figure 2. The region of a stable polymorphism when there is additive and opposite selection in the two sexes for autosomal genes (between the broken lines) and for X-linked genes (between the solid lines). *s_f* indicates the amount of selection against genotype *A₁A₁* in females and *s_m* indicates the amount of selection against *A₂A₂* (for autosomal genes) or *A₂* (for X-linked genes) in males.

0.111 for a stable polymorphism. It is noteworthy that the breadth of these conditions is similar to that for polymorphism because of selection in different environments (Levene 1953). Sex-dependent habitat selection, even without differential selection in the two sexes, may enhance the conditions for the maintenance of polymorphism (Hedrick 1993).

For X-linked genes or genes in haploid–diploid organisms, selection may greatly differ in the two sexes, acting in a haploid manner for males and a diploid manner for females. A stable polymorphism is also possible in this case when selection is acting in opposite directions in the two sexes (fitnesses of genotypes *A₁* and *A₂* in males are 1 – *s_m* and 1) and the conditions are

$$\frac{s_m}{1 - \frac{1}{2}s_m} > s_f > \frac{s_m}{1 + \frac{1}{2}s_m} \tag{10b}$$

The region in which there is a stable polymorphism, between the broken lines in Figure 2, is only 63% that of the analogous diploid case (Pamilo 1979; Hedrick and Parker 1997).

Sometimes when multiple selection components are influenced by variation at a single locus, there may be antagonistic pleiotropy, in which there is a negative correlation between different selection components (e.g., one allele at a given locus results in low viability and high fecundity, and another allele results in low fecundity and high viability). Such fitness arrays have been suggested as a mechanism for maintaining genetic variation and

are sometimes thought to be important in both life-history theory. However, the conditions for maintenance of polymorphism at a gene by antagonistic pleiotropy often are quite restrictive (Rose 1982; Curtsinger et al. 1994; Hedrick 1999) so that the general evolutionary significance is unclear.

Hedrick (1999) also examined the impact of a number of other factors on the maintenance of a polymorphism by antagonistic pleiotropy and concluded that the conditions were even more restrictive when there was sex-limited selection, for example, the reproductive effects are only in one sex such as female fecundity or male-mating success. In addition, inbreeding or finite population size also reduces the likelihood of a balanced polymorphism. Curtsinger et al. (1994) suggested that the only major exception to these restrictive conditions is when there is a reversal of dominance so that the heterozygote is closest to fitness to the favored homozygote for both traits. However, they suggested that the likelihood that dominance is commonly reversed for pleiotropic traits at a given gene is quite low. When the extent of selection is high, then the conditions for maintenance of polymorphism are also broader. For example, Hedrick (2001) showed that there are broad conditions for a transgene to invade a natural population when it has male-mating advantage, even though it has a viability disadvantage. A similar model (Hedrick 2003) suggested that the potential for maintenance of polymorphism of the recessive, detrimental disease albinism in Hopi Indians is unlikely from a balance of viability selection and male-mating advantage.

Genes that have opposite selective effects in females and males have been called sexually antagonistic genes (Rice 1992; Rice and Chippindale 2001). In this case, there may be an evolutionary arms race between the two sexes in which they both change in response to the other but there is no net overall change. For example, there may be selection on a trait to increase female reproductive success that consequently reduces male viability. To counter this, there may be subsequent selection to increase male viability, but this may then reduce female reproductive success. Rice and Chippindale (2001) suggest that there is sexual antagonism in fitness for various mutants until a variant is generated that allows each sex to evolve a value that is reflective of its gender-specific fitness optimum.

Theoretically, Rice (1984) predicted that sexually antagonistic genes are likely to be on sex chromosomes (Gibson et al. 2002). For example, if a X-linked variant is favorable in males and is unfavorable and recessive in females, then the initial positive selection in males will be much stronger than the negative selection in females (Rice 1984; Charlesworth et al. 1987). On the other hand, if a X-linked variant is favorable and dominant in females and unfavorable in males, then the initial positive selection in females will be much stronger than the negative selection in males (for an introduction to these ideas, see Vicoso and Charlesworth 2006).

Extensive recent microarray studies have found that many genes are expressed primarily in one sex in *Drosophila*, humans, mice, chickens and *Caenorhabditis elegans* (reviewed in Vicoso and Charlesworth 2006; Kaiser and Ellegren 2006). There appears to be an excess of female-biased genes and a deficiency of male-biased genes on the X chromosome in both *Drosophila* and *C. elegans* and in chickens there is an overrepresentation of male-specific genes on the Z chromosome (Kaiser and Ellegren 2006). However, the patterns are complicated and, for example, spermatogonial genes in mice that are expressed early are enriched on the X chromosome whereas those that are expressed later are depleted (Khil et al. 2004).

A number of additional considerations are related to sex-dependent selection. For example, selection on variants on X chromosomes is stronger in males because of haploid selection, assuming that favorable variants are recessive; therefore, it would be expected to result in an expected faster rate of evolution (Charlesworth et al. 1987; Vicoso and Charlesworth 2006) and a lower genetic load (Hedrick and Parker 1997). However, the evolution rate predictions are dependent upon the dominance of advantageous and detrimental variants and the pattern and intensity of selection for sexually antagonistic genes. The data at this point are rather mixed (Vicoso and Charlesworth 2006) and a recent survey in *Drosophila* found no evidence for a faster rate of evolution on the X chromosome (Thornton et al. 2006). In addition, selection for genes on the Y chromosome can only occur in males, suggesting that genes causing extreme male phenotypes would be on Y. Selection on mtDNA genes can only occur in females because males do not pass on their mtDNA genes but, as a result, detrimental mtDNA variants that are male limited may accumulate (Gemmell et al. 2004).

Gene Flow

Sex differences in dispersal (gene flow), and the potential evolutionary explanations for these patterns, have been the subject of many investigations and reviews (e.g., Clobert et al. 2001; Lawson Handley and Perrin 2007). As a result, here I will generally summarize and provide citations to access various aspects of this research.

ESTIMATION AND EVIDENCE

Differential gene flow in the two sexes can be estimated by direct methods (mark-capture, radio-tracking, etc.) that rely on field observation of individual movement. However, such dispersal may not always result in gene flow, that is, incorporation of genes into the breeding population and detection of complete dispersal distributions, including long-distance dispersal, are often difficult to obtain in natural situations (Koenig et al. 1996). Alternatives using genetic approaches have been employed to estimate movement in

the current generation. For example, examination of differences in post-dispersal sex-specific F_{ST} or assignment values have been proposed and used (Vitalis 2002; Goudet et al. 2002; Fontanillas et al. 2004).

Indirect methods can be used to estimate the cumulative effects of female and male gene flow in past generations and genetic markers with different patterns are useful to uncover sex differences in gene flow. Female gene flow has been estimated by examining the pattern of variation in the maternally inherited mtDNA and male gene flow by examining variation in the paternally inherited Y chromosome. The equilibrium F_{ST} values for these markers in an island model are

$$F_{ST(mt)} = \frac{1}{1 + 2N_{e,f}m_f} \quad (11a)$$

and

$$F_{ST(Y)} = \frac{1}{1 + 2N_{e,m}m_m}. \quad (11b)$$

where m_f and m_m are the rates of female and male gene flow and $N_{e,f}$ and $N_{e,m}$ are the female and male effective population sizes (see below). Obviously, a high sex-specific F_{ST} value may be the result of low gene flow, small population size, or both in that sex. These expressions can be solved for sex-specific values of Nm , the number of migrants of a given sex per generation. The time to reach these equilibrium values may be short if the sex-specific effective population size is small and the sex-specific gene flow is high or very long if the opposite is true (Crow and Aoki 1984).

Comparison of differentiation for mtDNA and Y chromosome markers has been made in a number of human populations (Wilkins 2006; Wilkins and Marlowe 2006). One of the first studies (Seielstad et al. 1998) found that differentiation on a global scale was much larger for Y than mtDNA markers and suggested that this was the result of much higher female than male gene flow. However, a more recent study (Wilder et al. 2004a) found that the level of global differentiation was similar for mtDNA and Y variants and suggested similar levels of female and male gene flow. On a more local scale in Thailand, it was found that for patrilocal tribes, in which women move to their mates' residence after marriage, resulted in a lower measure of differentiation for mtDNA than for Y, as expected (Oota et al. 2001). In contrast for matrilocal tribes, in which men move after marriage, there was a greater measure of differentiation for mtDNA than for Y (Oota et al. 2001). Further analysis of these data suggests that the differences are the result of 8 times as many male migrants in matrilocal as patrilocal tribes and 2.5 times as many female migrants in patrilocal as matrilocal tribes (Hamilton et al. 2005).

In plants, there may be gene flow from both gametes (nearly always male pollen) and zygotes (seeds, gene flow from both

sexes) and the effect of a given amount of gene flow is more effective from seeds because they are diploid and pollen is haploid. However, the amount of male gene flow from pollen may often be much larger, which can overcome this twofold difference in genetic content. Ennos (1994) showed that the overall (biparental) F_{ST} is related to that for maternally inherited markers, $F_{ST(m)}$, and paternally inherited markers, $F_{ST(p)}$, as

$$F_{ST} = \frac{F_{ST(m)}F_{ST(p)}}{F_{ST(m)} + F_{ST(p)} - 3F_{ST(m)}F_{ST(p)}}. \quad (12a)$$

In conifers, mtDNA is maternally inherited and cpDNA is paternally inherited. Latta and Mitton (1997) examined the variation in mtDNA and cpDNA in populations of limber pine, *Pinus flexilis*, mainly in north central Colorado. The value of $F_{ST(m)} = 0.679$, high mainly because a southern sample had a high frequency of mtDNA type not found in the other populations, and the value of $F_{ST(p)} = 0.013$, low because many of the same cpDNA types were found in all populations. When these values are used, the predicted F_{ST} from the above expression is 0.013; in other words, the high inferred level of male pollen gene flow is predicted to result in a low overall F_{ST} . The median value for 10 allozyme loci in the same populations was 0.016, not significantly different than that expected.

Using the level of overall F_{ST} and the maternal $F_{ST(m)}$, Ennos (1994) showed that the ratio of pollen gene flow (m_p) to seed gene flow (m_s) is

$$\frac{m_p}{m_s} = \frac{F_{ST(m)} - 2F_{ST} + F_{ST}F_{ST(m)}}{F_{ST}(1 - F_{ST(m)})}. \quad (12b)$$

(see also Hu and Ennos 1997; Hamilton and Miller 2003). In an oak species and five pine species (Ennos 1994; Latta and Mitton 1997), the pollen gene flow is much higher, and in two species, the oak species and limber pine, it appears to be more than two orders of magnitude higher. On the other hand, in two mountain ash species (Oddou-Muratorio et al. 2001; Bacles et al. 2004), pollen and seed gene flow rates are similar, apparently reflecting effective seed dispersal strategies by birds and mammals.

Finally, mtDNA and Y markers can be used to estimate the source of female and male founders for populations. The differences in ancestry are particularly striking in human populations in areas of European settlement or colonization. For example, 59% of the Y ancestry in Greenland Inuit samples was European (Scandinavian) whereas 0% of the mtDNA was European (Saillard et al. 2000; Bosch et al. 2003). Even more extreme in northwest Colombia, 94% of the Y ancestry was European (Spanish) whereas only 2% of the mtDNA ancestry was European (Carvajal-Carmona et al. 2000, 2003). Both of these examples support the conclusion that the contemporary ancestry of these populations descends from native women and a substantial proportion of European males.

EVOLUTIONARY CAUSE

The evolutionary explanations for sex-biased dispersal (gene flow) and data relating to these hypothesis are an important aspect of life-history variation in mammals, birds, plants, and other organisms and consequently been the subject of a number of reviews. As a result, here I will summarize these hypothesis and suggest that recent reviews (Clobert et al. 2001; Lawson Handley and Perrin 2007) provide an entrance to this extensive literature. Greenwood (1980) described the overall patterns of sex-biased dispersal and concluded that higher male dispersal and female philopatry were generally found in mammals and that higher female dispersal and male philopatry were generally found in birds. He suggested that “reproductive enhancement through increased access to mates or resources and the avoidance of inbreeding are important in promoting sex differences in dispersal” and that “the direction of the sex bias is a consequence of the type of mating system.”

Lawson Handley and Perrin (2007) divided up the factors hypothesized to influence evolution of dispersal into those that do, or do not, favor dispersal (Table 4). Mortality costs in dispersal, familiarity with natal area, and kin cooperation are factors that select against dispersing whereas variability in resources, kin competition, and inbreeding avoidance select for dispersal. They suggested that the observed pattern of dispersal is a balance between factors selecting for and against dispersing. And, because these factors are often different in females and males, dispersal levels are likely

to be different between the sexes. For example, male birds and female mammals may more likely defend resources and therefore disperse less. If one sex disperses, then inbreeding (inbreeding depression) can be avoided (Gandon 1999; Perrin and Mazalov 1999), although the impact may be complicated (Lehmann and Perrin 2003; Guillaume and Perrin 2006).

Lawson Handley and Perrin (2007) also evaluate examples of dispersal in mammals, 25 species with male-dispersal bias and 22 with female-dispersal bias. Although male-dispersal bias is thought to be more common in mammals, there are a number of phylogenetically clustered examples of female-dispersal bias in mammals. For example, female-biased gene flow found in some human studies seems exceptional. However, this may be a recent phenomena since the development of agriculture where males generally inherit their father’s land or herds (Wood et al. 2005; Wilkins and Marlowe 2006). On the other hand, as discussed above for matrilineal tribes in Thailand and populations in Greenland and Columbia, molecular data support the hypothesis that male gene flow was much greater than female gene flow.

POPULATION GENETIC IMPLICATIONS

As discussed, gene flow patterns may differ substantially between females and males. When there are different rates of gene flow in the two sexes, then for autosomal genes the arithmetic average over the two sexes,

Table 4. The factors proposed to cause decreased or increased selection for dispersal and some comments on how they may result in sex differences in dispersal (gene flow) (after Lawson Handley and Perrin 2007).

	Factor	Comments
Does not favor dispersal		
Mortality costs	Dispersers experience higher mortality crossing unfavorable habitats	Potential counter cost for cost of inbreeding depression
Familiarity with natal area	Dispersers do not know new habitat as well as residents and are not as able to compete for resources and defending territory	Important in male birds and some male mammals where defense of resources is important, important in female mammals
Kin cooperation	Dispersers may not benefit from cooperation with kin in acquiring mates or resources. Kin cooperation may keep out unrelated competitors	Important in social organisms, such as related female mammals rearing offspring and related male mammals acquiring and defending mates
Favors dispersal		
Resource availability	Given low correlation in resource availability over time and space, it is beneficial to disperse and find adequate resources	
Kin competition	Dispersing individuals may avoid competition with kin for mates or resources and leave natal area for relatives	
Inbreeding avoidance	Dispersal lowers the probability of mating with relatives and the cost of inbreeding depression	If one sex disperses to avoid inbreeding the other sex does not need to disperse

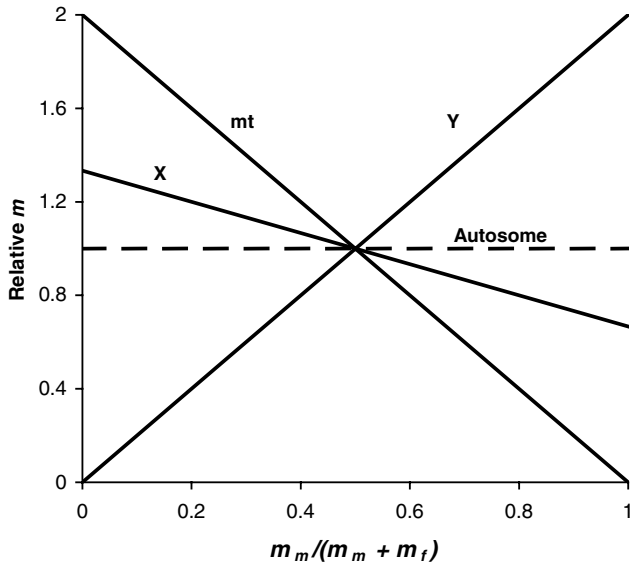


Figure 3. The amount of gene flow for genes on X chromosomes, Y chromosomes, and mitochondria, relative to that for genes on the autosomes, when the proportions of male and female gene flow varies.

$$\bar{m} = \frac{1}{2}(m_f + m_m) \tag{13a}$$

can be used. For X-linked genes or haplo-diploids, then

$$\bar{m} = \frac{1}{3}(2m_f + m_m). \tag{13b}$$

These gene flow values have higher female contributions when females disperse after mating (Berg et al. 1998).

The relative gene flow for these genes, as well as mtDNA and Y chromosome genes (see Table 2), are given in Figure 3. It is useful in plants to combine the impact of gene flow from pollen and seed (or gametic and zygotic) into one overall measure of the amount of gene flow. Because the genetic content of pollen is haploid and that of seeds is diploid, the overall gene flow is

$$\bar{m} = \frac{1}{2}m_p + m_s \tag{13c}$$

where the amounts of pollen and seed gene flow are m_p and m_s , respectively.

As we discussed above, different allele frequencies in the two sexes can result in an excess of heterozygotes over Hardy–Weinberg expectations. Prout (1981) showed that for an island model, sex differences in gene flow in an excess of heterozygotes as

$$H - 2\bar{p}\bar{q} = \frac{1}{2}(m_f - m_m)^2(\bar{p} - p_i)^2 \tag{14}$$

where p_i and \bar{p} are the frequencies of allele A_1 in subpopulation i and over all subpopulations. This excess is proportional to the

squared difference in gene flow parameters in the two sexes so that unless the differences are large, for example, all males are migrants ($m_m = 1$) and all females are nonmigrants ($m_f = 0$), the impact is not large (the theory of sex differences in gene flow are discussed by Wang 1997; Laporte and Charlesworth 2002).

Genetic Drift

Genetic drift, the chance loss of genetic variation due to small or finite population size, can be the result of continuous small or finite population size, bottlenecks, or founder effects. For all of these situations, there may be sex differences in genetic drift due to differences in the female and male effective population sizes, N_{ef} and N_{em} . In addition, the impact of mutation, recombination, selection, and gene flow in finite populations are often given as the product of the effective population size and the parameters for these factors. Assuming sex-specific values for all these factors, the general differences between the sexes can be given for mutation as $N_{ef}u_f$ and $N_{em}u_m$, for recombination as $N_{ef}c_f$ and $N_{em}c_m$, for selection as $N_{ef}s_f$ and $N_{em}s_m$, and for gene flow as $N_{ef}m_f$ and $N_{em}m_m$. For example, sex-specific impacts of mutation, recombination, selection, or gene flow may be increased or decreased by sex differences in the effective population size.

POPULATION GENETIC IMPLICATIONS

Genetic drift resulting from finite population size is recognized as an important factor in the evolution of small populations and for large, finite populations over evolutionary time for neutral variants. The expected extent of genetic drift is inversely related to the effective population size, a concept thoroughly reviewed by Cabarelo (1994). Here we introduce the general differences expected for genes with different types of inheritance and sex differences in effective population size. Considering different numbers of the two sexes, the effective population size for an autosomal gene is

$$N_{e.A} = \frac{4N_fN_m}{4N_f + N_m} \tag{15a}$$

where N_f and N_m are the number of females and males in the population, and $N_f + N_m = N$, the total number of adults in the population. Frequently, the number of males contributing progeny may be smaller than the number of females because some males mate more than once. When one male mates with all the females in a population, $N_{e.A}$ is a maximum of only 4. In other words, because each sex must contribute half the genes to the progeny, restricting the number of breeding males (or females) can greatly reduce the effective population size and increase genetic drift.

Nomura (2002) showed that for harem polygamy, assuming that all the females mate with one male (no variance in female

mating success) and that the males have a Poisson distribution in mating success, the effective population size becomes

$$N_{e,A} = \frac{4N_f N_m}{4N_f + N_m}. \quad (15b)$$

The ratio of equation (15a) to (15b) is $N_m/N + 1$ so that the ratio of these effective sizes is a decreasing function of the proportion of males. For example, if $N_m/N = 0.2$, then harem polygamy would reduce the effective size by 17%. This impact is further increased if the variance in male-mating success is greater than the variance given the Poisson distribution (Nomura 2002) (see also Nunney 1993).

It has often been assumed that in polygynous vertebrates, where one male controls a female group, such as in bighorn sheep or elephant seals, that he is the father of all the progeny (harem polygamy). However, the observed breeding behavior often is not supported genetically. For example, behavioral observations in the southern elephant seal estimated that the sex ratio was about 40 females per male but the effective sex ratio from genetic data was estimated to be only 4 or 5 females per male (Slade et al. 1998). The difference in these estimates appears to result from both an overestimate of breeding success in the behavioral estimate and the short time that a male is dominant (1 or 2 years).

For an X-linked gene (or one in a haplo-diploid organism), because females contain two-thirds and males one-third of the alleles, the effective population size is

$$N_{e,X} = \frac{9N_f N_m}{2N_f + 4N_m} \quad (16)$$

(Wright 1931; Cabarello 1995). If there are equal numbers of females and males ($N_f = N_m = 1/2N$), then $N_{e,X} = 3/4N$ because the males are haploid. In other words, the effective population size for an X-linked gene is generally expected to be 75% that of an autosomal gene in the same species. When there is only one breeding male for an X-linked gene, then the maximum $N_{e,X} = 4.5$, somewhat larger than for an autosomal gene. In some social Hymenoptera, there may be only one breeding female or queen so that the effective population size is a maximum of only 2.25. When there is harem polygamy, Nomura (2002) also showed that the effective size for an X-linked gene is reduced by variance in male-mating success.

The effective population size is a function of the variance in progeny number and the effective population size is

$$N_e = \frac{N\bar{k} - 1}{\bar{k} - 1 + \frac{V_k}{k}} \quad (17)$$

where \bar{k} and V_k are the mean and variance in the number of progeny. Using sex-specific values of \bar{k} and V_k for females and males, then N_e values for females (N_{ef}) and males (N_{em}) can be

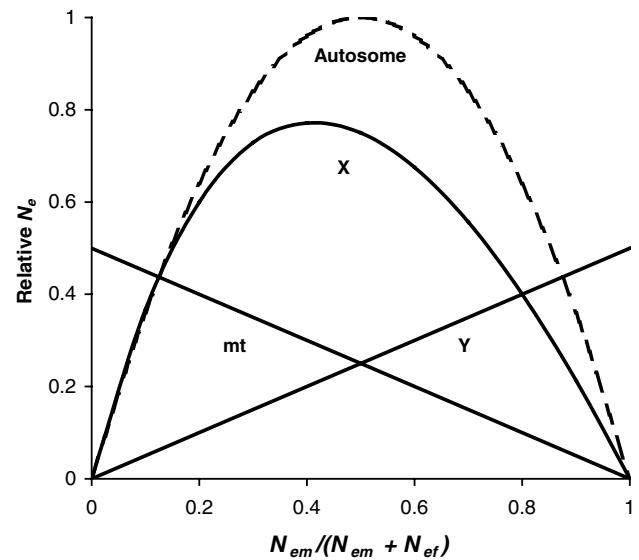


Figure 4. The effective population size for genes on autosomes, the X chromosome, the Y chromosome, and mitochondrial DNA, relative to that for genes on autosomes with equal sex ratios, when the ratio of male to female effective size varies.

calculated (Lande and Barrowclough 1987; Engen et al. 2007). The overall effective population size for an autosomal or X-linked gene can then be calculated by using N_{ef} and N_{em} in the equations above as given in Table 2.

The effect of different ratios of female and male effective population size on the relative effective population size for genes on different chromosomes is given in Figure 4. Notice that for autosomal genes when the ratio of the input of either sex is low, the overall effect is largest, unlike the additive effect for mutation, recombination, or gene flow. To determine when the effective population size for autosomal and X-linked genes is the same, we can set these equations equal to each other and find that when $N_{em} = N_{ef}/7$, $N_{e,A} = N_{e,X}$. Or, whenever $N_{em} < N_{ef}/7$, the effective population size for an X-linked gene is slightly larger than for an autosomal gene in the same population.

For genes that are inherited only through one sex such as mtDNA, cpDNA, and the Y chromosome, the effective population size for the appropriate sex determines the effect of genetic drift on those genes. In all of these cases, if there is an equal sex ratio, and random progeny production for both sexes, the expected effective population size is $N_e/4$ because these genes are transmitted in only one sex and they are haploid. Without these assumptions and because mtDNA and cpDNA are generally maternally inherited, their effective sizes are

$$N_{e,mt} = \frac{N_{ef}}{2}. \quad (18a)$$

If the number of males breeding or the male effective population size is small, then the effective size for such a gene may

actually be greater than for an autosomal gene in the same population (Fig. 4). For example, if N_m is 1, then N_e for an autosomal gene is a maximum of 4 but because N_{ef} can be much larger than 8, N_e for an organellar gene can be larger than for an autosomal gene. Interestingly, $N_{e,mt} = N_{e,A} = N_{e,X}$ when $N_{em} = N_{ef}/7$, that is, when $N_{em}/(N_{em} + N_{ef}) = 0.125$, and the effective population sizes for autosomal, X-linked, and mtDNA genes are the same.

The Y chromosome effective population size, and for mtDNA when it is inherited paternally as in conifers or mussels, is

$$N_{e,Y} = \frac{N_{em}}{2}. \quad (18b)$$

In organisms with a low male effective size, the effective size for such a gene could be much smaller than that of an autosomal gene in the same organism. Only if $N_{em}/(N_{em} + N_{ef}) > 0.875$ or > 0.8 is it larger for an autosomal or X-linked gene, respectively (Fig. 4). Wade and Shuster (2004) suggest that the variance in fitness may be much larger in males than in females (higher V_k) because of sexual selection. Therefore, N_{em} may be much smaller than N_{ef} and consequently $N_{e,Y}$ may be much smaller than $N_{e,mt}$.

Using simulations, Storz et al. (2001) estimated the impact of life-history variation in a baboon population and a tribal human population on the effective population size for genes with different inheritance. Although N_e/N was 0.33 and 0.79 for baboon and human populations, due primarily to variance in male fitness, X, Y, and mtDNA effective population sizes were not different from the expected ratios with autosomal N_e (0.75, 0.25, and 0.25) assuming Poisson variance in reproduction. These results are consistent with the theoretical conclusion of Charlesworth (2001) that extreme differences between the sexes in survival and fecundity are necessary to cause major departures from these expected ratios.

With the availability of genetic markers on chromosomes with different inheritance, in recent years there have been a number of studies examining the effective population and the amount and pattern of genetic variation (Hellborg and Ellegren 2004; Sundström et al. 2004; Balaesque et al. 2006; Eriksson et al. 2006; Lawson Handley et al. 2006; Baines and Harr 2007). In many such studies, it is difficult to disentangle the additional impact of differences between the markers in selective sweeps, background selection, and other sex-specific processes (Betancourt et al. 2004). Wilder et al. (2004b) examined variation in human mtDNA and nonrecombining Y chromosome genes and estimated that the time to most recent common ancestor for mtDNA is twice as old as for the Y. As a result, they concluded that this difference appears to result in an approximate twofold larger effective population size for females than for males.

Conclusions

Sex differences in the evolutionary factors, mutation, recombination, selection, gene flow and genetic drift, which determine evo-

lutionary change are often quite large. However, the patterns of these differences and the evolutionary and mechanistic forces suggested to influence these sex differences are generally restricted to only one factor. In other words, there does not seem to be a unifying theme or similar cause for the sex differences over multiple evolutionary factors.

There is generally a higher mutation rate in males than females and this difference has been found using both direct and indirect estimation approaches. The higher mutation rate in males appears to be generally related to the greater number of cell divisions leading to male gametes and there is a general increase in this difference with an increase in generation length. However, mutation rates are also a function of the type of mutation, the particular gene or genomic region, and organism, suggesting that much remains to be understood about the sex differences in mutation.

Sex differences in recombination have long been explained by the Haldane–Huxley rule that when one sex has no recombination, it is the heterogametic sex. When there is recombination in both sexes, there are a number of exceptions to this association, suggesting that other factors are important. A number of evolutionary hypotheses have attempted to explain these differences but it is not clear when and if they are important factors influencing sex differences in recombination. In addition, there is evidence suggesting that recombination rates vary over different genomic regions within a species, potentially indicating that there is no general evolutionary explanation for sex differences in recombination.

Sex differences in selection occur for particular loci. These sex differences in selection can result in polymorphism for both autosomal and X-linked genes and a faster rate of evolution for X-linked genes. In addition, sex-dependent selection may result in antagonistic pleiotropy and sexually antagonistic genes. How prevalent such genes are in the total genome is generally unknown but they may be genes undergoing strong selective effects. Further, sex-dependent selection may have strong impacts on genes on the sex chromosomes.

Unlike mutation and recombination, which result in indirect or secondary selection, sex differences in gene flow have the potential to have large selective differences and result in fast evolutionary change. Although the genetic basis of sex-dependent differences in gene flow is not generally known, it could present other genes with an environment or situation in which strong selection could occur, particularly if genes are sex limited in their expression. Because dispersal is a fundamental aspect of natural history, there has been extensive long-term interest in sex differences in dispersal and the development of numerous evolutionary hypotheses to explain these differences. For a given species, there may be a number of costs and benefits to dispersal and how these result in sex-specific differences appears complicated.

Finally, sex differences in genetic drift (effective population size) may be large for particular species and the sex with the lower effective population size dominates the impact of genetic drift. This nonlinear impact is particularly important when examining the joint effects of genetic drift with mutation, recombination, selection, or gene flow. For example, sex differences in these other factors may be significantly influenced by positively or negatively correlated sex differences in genetic drift.

The primary impact of sex-dependent differences in mutation, recombination, and gene flow for evolutionary change and genetic variation is that they cause the mean values of these factors to increase or decrease. The sex origin of mutation, recombination, or gene flow for autosomes is quickly lost in the following generations. In other words, sex-specific differences from these factors are on the mean values for autosomal genes but they may have important differential impact on nonautosomal genes. On the other hand, the overall effects of sex-specific selection and sex-specific genetic drift generally are not the result of their mean effect because of the nonlinear impact of sex differences in these evolutionary factors. Particularly, for situations with nonlinear effects or where multiple factors simultaneously are important, models with sex-dependent values of evolutionary processes should be used for analysis and interpretation.

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