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EVOLUTIONARY GENETICS AND GENETIC VARIATION OF HAPLODIPLOIDS AND X-LINKED GENES

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ABSTRACT

The evolutionary genetics of haplodiploids and X-linked genes share many features and are different from diploid (autosomal) genes in many respects. For example, the conditions for a stable polymorphism, the amount of genetic load, and the effective population size are all expected to be quite different between haplodiploids or X-linked genes and diploids. From experimental data, the genetic load for X-linked genes is much less than autosomal genes and appears less for haplodiploids than for diploids. The observed amount of molecular variation for haplodiploids is much less than that for diploids, even more so than predicted from the differences in effective population size. Extensive recently published data suggest that the differences in variation for X-linked and autosomal genes for *Drosophila*, mice, and humans are consistent with the differences predicted theoretically based on the relative effective population sizes.

INTRODUCTION

The evolutionary genetics of all genes in haplodiploid species and X-linked genes in diploid organisms have many similarities and differ from autosomal genes in diploid organisms in a number of ways. In this review, we examine the commonalities of the evolutionary genetics of these two systems, particularly in light of recent molecular, theoretical, and experimental developments. Evolutionary factors such as gene flow and genetic drift should be identical in autosomal and X-linked genes in the same organism, except for some intrinsic differences between the two groups of loci, so that autosomal genes

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act as a "control" for the amount of genetic variation and the impact of other evolutionary factors, such as selection and mutation, in X-linked genes. For haplodiploids, no such direct comparison is possible, and for evaluation of levels of genetic variation, diploid insects, which may have many other differences from haplodiploids, are the best standard.

More than 15% of all animal species are haplodiploid (129), most of them in the Hymenoptera (ants, bees, and wasps), but this number includes some other species, such as insects in the Thysanoptera (thrips), some Coleoptera (beetles), and some Homoptera (whiteflies and scales), as well as some arachnids (mites) and rotifers (34, 67). In most organisms with X chromosomes, less than 10% of the genes are X-linked and the remainder are autosomal, but in some species the proportion is much larger, e.g. about 38% of the euchromatin (and presumably the expressed genes) of *Drosophila robusta* is X-linked (18), while in *D. melanogaster* approximately 20% of the genes are on the X chromosome (36).

Several major similarities exist for genes in haplodiploids and X-linked genes.

1. For autosomal genes in diploids, both sexes inherit alleles equally from both parents. This is also true for females in haplodiploids and for females for X-linked genes. (We assume the homogametic sex is the female and the heterogametic sex is the male but recognize that in birds, snakes, and butterflies, the chromosomal constitution of the sexes are reversed; in those cases, the same conclusions for X-linked genes would hold, but the sexes would be reversed.) However, unlike diploids (the term diploids is used synonymously with autosomal genes in diploids hereafter), males for haplodiploids or X-linked genes inherit all their genes from their mother. For haplodiploids, this occurs because haploid males are the consequence of unfertilized eggs, and for X-linked genes, it is the consequence of not receiving an X-chromosome from the male parent. Thus, males in haplodiploids have no father and, although males do not inherit X-linked genes from their father, they do inherit autosomal and Y-linked genes from him.

2. Female haplodiploids or females with X-linked genes have twice as many copies of the genes as do males, a factor important in determining overall allelic frequencies, mutation rates, and rates of recombination.

3. Because females are diploid in haplodiploids and for X-linked genes and, as a result, can be heterozygous, selection is modeled in the same manner as for diploid genes with varying levels of dominance. On the other hand, because males have only one copy of a gene, selection in males is modeled in the same manner as haploid or gametic selection.

We do not have space to discuss some interesting aspects of the evolutionary genetics of haplodiploids or X-linked genes. Some important topics in haplodiploids, most related to social behavior, omitted here, include

the evolution of sociality and sex ratios (12, 39a, 65, 123, 137), measures of relatedness (129), evolution of social organization (142), colony-level selection (113, 125, 126), sex-determining loci and production of diploid males (31, 32, 120, 130), and selection on worker-produced males (119). Similarly, we do not discuss some important topics related to X-linked genes, such as reproductive isolation and speciation (77, 159, 168, 172), meiotic drive (41, 89, 97), male-driven evolution (93, 149), distribution of transposable elements over chromosomes (24, 48, 103), and X-linked human genetic diseases (99). In addition, dosage compensation (6, 94) and quantitative genetics (79, 92, 116), topics related to understanding the evolutionary genetics of both haplodiploids and X-linked genes, are not discussed.

We first introduce some basic evolutionary genetic theory relating to a particular evolutionary factor (or factors) and give references for more detailed theoretical coverage. We also give pertinent experimental examples and molecular data, when available, that are relevant to the evolutionary genetic theory. Finally, we discuss the amount of molecular variation observed in various groups of haplodiploids and that observed for X-linked and autosomal genes. We then discuss possible evolutionary genetic explanations for these observations.

EVOLUTIONARY GENETICS

Allelic and Genotypic Frequencies

The estimation of allelic frequencies and their variances in females and males for a haplodiploid or a X-linked gene is straightforward and follows estimation for genes in diploid and haploid organisms, respectively (92). Because two thirds of the genes are in females and one third in males, the estimate of the mean allele frequency must be weighted accordingly. However, if the initial frequencies in the two sexes differ (127) and there are nonoverlapping generations, the allele frequencies in the two sexes will oscillate above and below the mean frequency and dampen to the mean frequency in a few generations (the difference in allelic frequency between the sexes is halved each generation) (81, 92). However, if there are overlapping generations, then allelic differences in frequency between the sexes generally dampen more quickly (33, 106). Clegg & Cavener (29) examined oscillations between the sexes in allele frequency for two X-linked allozyme loci 64 map units apart in *Drosophila melanogaster* and found their observations generally consistent with these predictions.

If there are different allelic frequencies in the two sexes, this leads to an expected excess of heterozygotes and a deficiency of homozygotes compared to Hardy-Weinberg proportions. With an observed heterozygosity of H, two alleles A_1 and A_2 with mean allelic frequencies of $\overline{p}$ and $\overline{q}$, and with frequencies of A_2 in females and males of q_f and q_m, respectively, the expected excess of heterozygotes is $H-2\overline{pq} = 2(4q_f - q_m)(q_f - q_m)/9$ (72). For example, if

the difference in allelic frequencies between the two sexes is 0.2, the excess of heterozygotes is 0.031. When the allelic frequencies are near 0.0 or 1.0, the expected heterozygosity is low, and there can be a considerable proportional excess of heterozygotes. If there is substructure to the population, a deficiency of heterozygotes may result (72, 92), which could cover up any excess of heterozygotes from different allelic frequencies in the sexes.

Selection

With directional selection and relatively small selective differences, allelic frequency differences in the two sexes converge rather quickly (58, 107). Assuming that the allelic frequencies in the two sexes are similar and that dosage compensation (defined here as when the difference in fitness between the two male genotypes is same as the difference in fitness between the two homozygotes in females), then the rate and pattern of response is approximately one third faster in haplodiploids or X-linked genes than in diploids (68) and is faster for all levels of dominance (2). This increased response results because all alleles are exposed to selection in males for haplodiploids and X-linked genes and not protected from selection in heterozygotes as in diploids. Further, a recessive detrimental allele is never covered up in males by a dominant allele, suggesting that the frequency of detrimentals for haplodiploids or X-linked genes should be lower than for diploid genes (see below). Also, a favorable allele should increase in frequency faster in a haplodiploid or an X-linked gene than in a diploid, in both an infinite and a finite population (2, 23; see also 70). Fisher's fundamental theorem, i.e. the rate of change in fitness is equal to the variance in fitness, holds well in haplodiploids or X-linked genes when there are relatively small selective effects and dosage compensation (68).

However, when there is an initial difference in the allelic frequency between the sexes and nonoverlapping generations, these differences may be perpetuated during selection. An experimental example is given in Figure 1, where the observed and expected change in allelic frequency for the X-linked mutant *w* (white) in *D. melanogaster* with equal initial allelic frequency in the two sexes (Figure 1*a*) is contrasted with the initial frequencies being different (Figure 1*b*) (69). In both examples, the *w* allele is rapidly eliminated, but the elimination is slightly slower when the initial frequencies are different. Both the oscillations in allelic frequency and the difference in rate of elimination are predicted theoretically using independently estimated fitness components (69).

Many researchers have determined the conditions for a stable polymorphism for genes in haplodiploids or X-linked genes (40, 60, 67, 124, 128, see other references in 67). When there is no selection at a particular gene in the males, i.e. the trait is sex-limited to females (83), the condition for a polymorphism in haplodiploids or X-linked genes is heterozygous advantage (in females), the

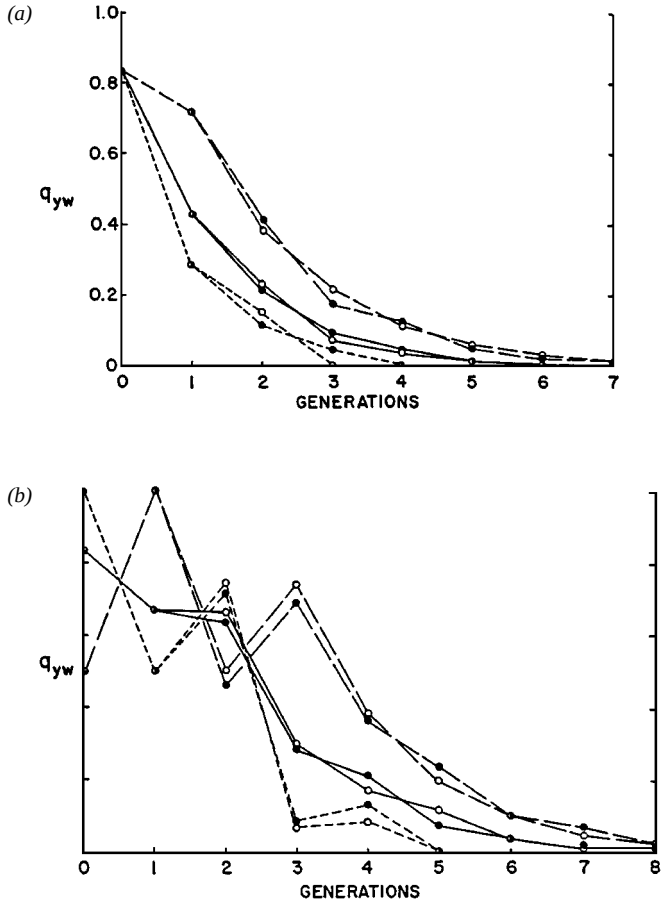

Figure 1 The change in frequency for the X-linked mutant white (*w*) when (*a*) there are equal initial frequencies in the two sexes and (*b*) when the initial frequencies are different. The *open* and *closed circles* indicate experimental results and theoretical predictions, respectively. The *solid*, *short-broken*, and *long-broken lines* refer to the mean, female, and male allelic frequencies, respectively (from 69).

same as for a diploid gene. Although these conditions are equivalent to those in diploids, the extent of selection (only in one sex) is lower so that, in combination with genetic drift or gene flow, the impact may be less.

With selection also acting in males, heterozygous advantage in females is neither a necessary nor a sufficient condition for a stable polymorphism. Figure 2a (after 124) gives the example for haplodiploids or X-linked genes where there is heterozygous advantage in females and differential selection in males (the relative fitness values are $1 - s_1$, 1, and $1 - s_2$ for genotypes A_1A_1, A_1A_2, and A_2A_2, respectively, in females (both haplodiploid or X-linked and diploid) and diploid males, and $1 - s_1$ and $1 - s_2$ for haplodiploid or X-linked males with genotypes A_1 and A_2, respectively). For diploids under this fitness regime, the whole region allows a stable polymorphism (s_1, $s_2 < 1.0$). However, for haplodiploids and X-linked genes, the region (given between the broken curved lines) is much smaller, only 58% that for diploids. Intuitively, this can be understood by realizing that when selection is very different between the two male genotypes (the upper left and lower right corners of Figure 2a), this strong directional selection overcomes the heterozygote advantage in females.

In addition, a stable polymorphism can be maintained if there is selection in opposite directions in the two sexes even though there is no heterozygote advantage in either sex (Figure 2b; the relative fitness values here are 1, $1 - s_1/2$, and $1 - s_1$ for genotypes A_1A_1, A_1A_2, and A_2A_2, respectively, in both haplodiploid or X-linked and diploid females, $1 - s_2$, $1 - s_2/2$, and 1 for diploid males with genotypes A_1A_1, A_1A_2, and A_2A_2, respectively, and $1 - s_2$ and 1 for haplodiploid or X-linked males with genotypes A_1 and A_2, respectively). When the two sexes have selection in opposite directions, then a stable polymorphism in a diploid can be maintained if the harmonic means of the homozygotes are less than those of the heterozygote (solid curved lines in Figure 2b, 85). For haplodiploids or X-linked genes, the region of stability is smaller (broken curved lines)—63% that in diploids (124). When there is differential selection between the sexes, the allelic frequencies at equilibrium may be greatly different (see 72 for an example) and, as a result, before selection there may be an excess of heterozygotes over Hardy-Weinberg expectations.

In both these theoretical cases, dosage compensation is assumed, i.e. the same difference occurs between the fitnesses in the two male genotypes as between the two female homozygotes. If there is no dosage compensation, and the difference between the fitness of the male genotypes is one half that of the female homozygotes, the region of a stable polymorphism is intermediate between those given for haplodiploids and diploids in Figure 2*a* and is smaller than that given for haplodiploids in Figure 2*b*.

Perhaps the most convincing example of a balanced polymorphism for a haplodiploid or an X-linked gene is that for the *Pgm*-3 locus in the fire ant

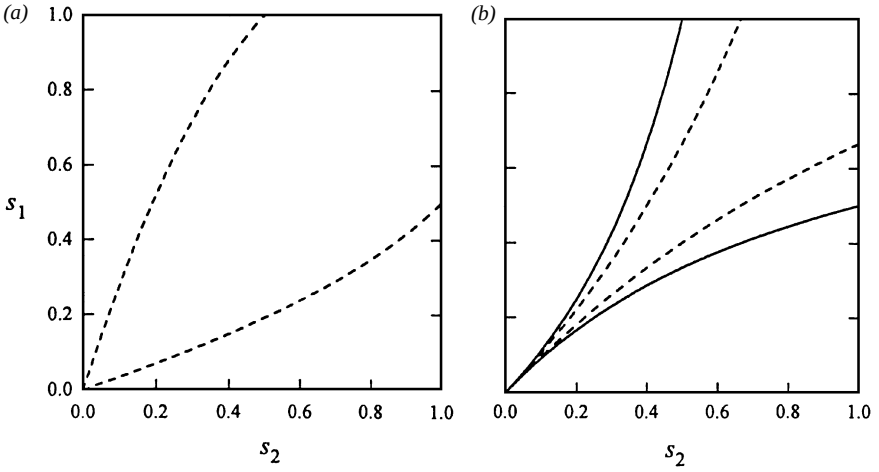

Figure 2 Regions of stability for a haplodiploid or X-linked gene (between the *curved broken lines*) or an autosomal gene [the *whole square* or between the *solid curved lines* for (*a*) and (*b*) (adapted from 124)] when there is heterozygote advantage in the females (*a*) and when there is selection in different directions in the two sexes (*b*). See the text for the definition of the selection coefficients (s_1 and s_2 values) for the two different situations.

(*Solenopsis invicta*), in which there is strong selection against homozygous *Pgm*-3^a queens in polygynous populations and selection for this genotype in monogynous populations (141, 143). However, to describe this situation completely, a model with both selection and gene flow simultaneously is necessary (for a general theoretical introduction to selection and gene flow in haplodiploids or X-linked genes, see 114). Significant differences between the sexes in allelic frequency have been described for three of six allozyme loci examined in red wood ants; these differences may be the result of differential selection although it is not known if there is a stable polymorphism (127). Selection appears to significantly influence the maintenance of polymorphism for the X-linked allozyme loci G6PD and 6PDG in *D. melanogaster* (10). G6PD deficiency in humans, also X-linked, has long been thought to be associated with resistance to malaria (95, 105). Recently, an approximately 50% reduction in risk for severe malaria has been shown for both female heterozygotes and males with G6PD deficiency (144). There may have been a counterbalancing selective disadvantage of G6PD deficiency in the past, but at present in areas with endemic malaria, there appears to be overall directional selection favoring G6PD variants.

Effective Population Size

A haplodiploid or an X-linked gene has fewer copies of a given gene (only one copy in males) in a population than does a diploid gene. If random sampling

of gametes is assumed, the effective population size for diploids is $N_{e.d} = 4N_f N_m/(N_f + N_m)$ and that for haplodiploids or X-linked genes is $N_{e.hd\text{-}X} = 9N_f N_m/(2N_f + 4N_m)$, where N_f is the number of breeding females and N_m is the number of breeding males (170). With equal sex ratios, the effective population size for haplodiploids or X-linked genes is $3/4$ that of diploids.

Crozier (37) observed that the ratio of the haplodiploid or X-linked to diploid effective population sizes varies for different sex ratios and that the ratio approaches $9/16$ with an extreme male-biased ratio and $9/8$ with an extreme female-biased sex ratio (the two effective populations sizes are equal at $7N_m/2$ when $N_f = 7N_m$). Several other authors (111, 168) have pointed out that differences in effective population size (and the resulting heterozygosity under the neutral model) between haplodiploids or X-linked genes and diploids depend on the mating system. The effective population sizes may be small at these sex-ratio limits: $N_{e.d}$ approaches four times the number of the less common sex at both extremes, and $N_{e.hd\text{-}X}$ approaches $9N_f/4$ for the extreme male-biased sex ratio and approaches $9N_m/2$ for extreme female-biased sex ratio.

An intuitive explanation for these ratios at the sex-ratio limits is as follows. When there are many more males than females, the diploids have a larger effective size because the contribution from the haploid males approaches one half that of diploid males; hence the low ratio value of $9/16$. When there are many more females than males so that females have a larger effective size, the female contribution is two thirds for the haplodiploid and only one half for the diploid; hence the ratio approaches the value greater than unity of $9/8$. Sex ratios in haplodiploids vary from high female-to-male in some parasitoids to high male-to-female in honey bees (65, 137). However, the effective number of matings for a given female may be generally small (12) so that the effective sex ratio may not deviate greatly from unity, thereby making the expected ratio of effective population sizes for haplodiploids and X-linked genes to that for diploids, all else being similar, close to $3/4$.

Several recent detailed theoretical treatments on the effective population size in haplodiploids and X-linked genes have included consideration of unequal family sizes and the sex of both the parent and offspring (16, 109, 134, 161). When there are overlapping generations, the equations in these references still hold if standardized by time to first reproduction and by letting N_f and N_m be equal to the number of females and males entering the breeding age in that time interval (75, 136). We discuss two of the more interesting predictions from these theoretical treatments.

Effective population size is a function of the variance in progeny number per parent and it is generally assumed to have a Poisson distribution, the expectation from random sampling of gametes. For a diploid gene, if the variances in progeny numbers are zero (all families have the same number of progeny),

then $N_e = 2N$, where N is the number of parents (170). For a haplodiploid or a X-linked gene, the effect is slighter greater: $N_e = 9N/4$, when the variances in progeny number are zero (16). The higher value for haplodiploids or X-linked genes appears to occur because there is no segregation in these males. However, the two sexes have greatly different influences on this effect for haplodiploids or X-linked genes. When the variance in male progeny is Poisson and that for female progeny is zero, $N_e = 3N/2$; with the variance in male progeny zero and the variance in female progeny Poisson, $N_e = 9N/10$ (165). In other words, N_e is increased much more by a smaller variation in the number of female progeny per family than that in male progeny.

When there is inbreeding in a diploid population, the effective population size is $N_{e.d} = 4N_f N_m/[(1+\alpha)(N_f + N_m)]$ (17), where α is the equilibrium inbreeding coefficient (73). When α is at its maximum of unity, $N_{e.d}$ is reduced to half its value when there is no inbreeding ($\alpha = 0$). For a haplodiploid or an X-linked gene with inbreeding, $N_{e.hd\text{-}X} = 9N_f N_m/[2N_f + 4(1+\alpha)N_m]$ (163). When α is unity, $N_{e.hd\text{-}X}$ is reduced to 0.60 its value when there is no inbreeding. For a haplodiploid or an X-linked gene, the effect of inbreeding on effective population size is also a function of the sex ratio. When there is a high female-to-male sex ratio, there is no effect of different inbreeding levels on the effective population size, which is $9N_m/2$ for all α values. For a high male-to-female sex ratio, the effective population size is reduced from $9N_f/4$ with random mating to $9N_f/8$ when $\alpha = 1$, similar to the effect for diploids. At these extreme sex ratios, the effective population sizes could be small if the numbers of the rarer sex are low.

Inbreeding

Our discussion of inbreeding (and the related concept, "relatedness") will not be lengthy because relatedness is the subject of a review in this volume (129). Close inbreeding, particularly high levels of brother-sister mating, appears to be common in some wasps (66, 161) and ants (134). Several aspects of inbreeding distinguish haplodiploids or X-linked genes from those of diploids.

Because males are haploid, they cannot be inbred (identity by descent of two alleles can occur only in diploids). When one assumes the inbreeding coefficient in males is zero and averages inbreeding over both sexes, then haplodiploids and X-linked genes have lower expected inbreeding than do autosomal genes. The inbreeding coefficient calculated from a pedigree for haplodiploid or X-linked females may be different from that calculated for an autosomal gene. A procedure to calculate the inbreeding coefficient (f) from a pedigree for a haplodiploid or an X-linked gene is to use the expression $f = \Sigma[(1/2)^{N_f}(1+f_{CA})]$, where the summation is over all common ancestors (CA), N_f represents the number of females in the chain linking the parents of the inbred individual to the

common ancestor, and f_{CA} is the inbreeding coefficient in the common ancestors (35, 92, 170). Two important aspects differentiate this from the inbreeding coefficient for diploid genes, namely, only female ancestors are counted and if there are two or more consecutive male ancestors in the chain (for X-linked genes; haplodiploid males do not have a male parent), there can be no inbreeding. For example, if two half sibs mate and their common parent is a male, then there is no possibility of inbreeding in their offspring for an X-linked gene, even for female offspring.

In some human populations, the differences between sexes of the ancestors of two related individuals may actually make the inbreeding coefficient for an X-linked gene higher than for an autosomal gene. For example, first-cousin matings, which give an inbreeding coefficient of 1/16 for autosomal genes, give different inbreeding coefficients for females for the four different types of first-cousin matings, depending upon the sex of the parents of the first cousins. A first-cousin mating can result in an inbreeding coefficient of 0 for the two types of matings in which the parent of the male first cousin is a male, 1/8 when the parent of the male first cousin is a female and the parent of the female first cousin is a male, and 3/16 when both parents of the first cousins are female (the last is called a matrilineal or matrilateral cross-cousin mating, 145). Estimates of the inbreeding coefficients in a large number of couples of different ages, religions, castes, etc from South India were quite high for human populations (138, 145). Further, the inbreeding coefficient was significantly higher for X-linked than for autosomal genes: 0.051 versus 0.023 in rural Andhra Pradesh (145), 0.0411 versus 0.0371 in rural Tamil Nadu (138), and 0.0228 versus 0.0205 for urban Tamil Nadu (138). These differences were attributed to a cultural preference for matrilineal cross-cousin marriages over the other types of first-cousin marriages.

For diploids, the coefficient of relatedness in the parents of an inbred individual is twice the inbreeding coefficient for an inbred offspring from that mating (92, 169). This same relationship holds for two sisters in haplodiploids, as used in the development of kin selection theory (63, 64). However, for individuals of different ploidy levels, the direction of the comparison influences the level of relatedness. In haplodiploids and X-linked genes, there is an asymmetry in the relatedness of individuals of different sexes. For example, sister-to-brother relatedness is 1/2 while brother-to-sister relatedness is only 1/4 (for further discussion, see 128 and references therein).

Chapman & Stewart (20) surveyed seven polymorphic allozyme loci in a solitary wasp and used deviations from Hardy-Weinberg proportions to estimate the level of inbreeding. For all the loci, there was an extreme deficiency of heterozygotes; the estimated proportion of full-sib mating at inbreeding equilibrium (73) necessary to cause these deviations was 0.913. Because the inbreeding equilibrium is reached only after approximately five generations from full-sib

mating, these high estimates indicate that similar levels of full-sib mating appear to have been present, without interruption, for a number of generations.

Two or More Loci

The estimation of gametic frequencies for two or more loci in diploids is complicated because it is not possible to observe directly the phase of the gametes in genotypes heterozygous at two or more loci, making it necessary to use a maximum likelihood procedure (74, 154). However, for haplodiploids or X-linked genes in males, the phase of all gametes can be observed directly, and the estimation procedure is identical to that for haploids or observed gametes (72; see 122 for an application in a bee population). The estimation of gametic frequencies over both sexes for a haplodiploid or an X-linked gene, if it assumed that there is no difference in gametic frequencies between the sexes, can use the estimates in males in the maximum likelihood estimation for females (154).

Because there is no recombination in males for both haplodiploids and X-linked genes ($c_m = 0$), and two thirds of the gametes are produced by females, the mean recombination rate is $\bar{c} = 2c_f/3 + c_m/3 = 2c_f/3$, or one third less than the rate for autosomal genes. (An interesting contrast is in *Drosophila* species that have no recombination in males for any genes so that the rate of recombination between autosomal genes, $c_f/2$, is lower than that for X-linked genes.) Therefore, the rate of decay of gametic or linkage disequilibrium (nonrandom association of alleles at different loci) for two loci, assuming equal gametic frequencies in the two sexes, is $D_t = D_0(1 - 2c_f/3)^t$, where D_t is the disequilibrium in the tth generation. If the gametic frequencies in the two sexes differ, the treatment is substantially more complicated (7, 29, 171). However, a difference in gametic frequencies in the two sexes increases the proportion of double heterozygotes somewhat and consequently increases the number of new recombinant gametes and the rate of decay of gametic disequilibrium. Further, with overlapping generations, the predicated rate of decay of disequilibrium is even further complicated (29, 135), as illustrated by the observations in experiments for two X-linked allozyme loci in *D. melanogaster* (29).

Hedrick (69) examined the change in the frequency of two tightly linked genes ($c_f = 0.015$), yellow (y) and white (w), on the X chromosome in *D. melanogaster* (Figure 3). Starting in maximum gametic disequilibrium and using estimates of the relative fecundity and mating ability of the different genotypes, the change in gamete frequencies and amount of disequilibrium over the 21 generations of the experiment was quite closely predicted, using independently estimated fitness components. In particular, the observed increase in the frequency of the wild-type gamete (++), which was produced by recombination during the experiment, was close to that predicted.

The maintenance of polymorphism, with or without disequilibrium, by two-locus selection depends on the maintenance of polymorphisms at both loci, a

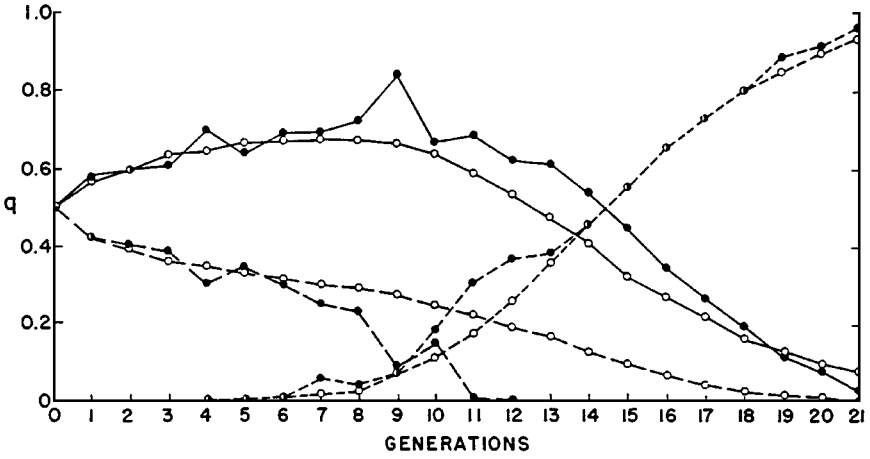

Figure 3 Frequency of gametes in males over generations when the population was initiated with equal numbers of $+w$ and $y+$ gametes where *w* is the mutant white allele, *y* is the mutant yellow allele, and + is the wild type for the two genes. The *solid, long broken,* and *short broken lines* indicate the frequencies in males of $+w$, $y+$, and $++$ gametes, respectively, and the *closed* and *open circles* indicate observed and simulated values (from 69).

condition that is more restrictive in haplodiploids or X-linked genes than in diploids, as discussed above. With selection limited to females, the conditions reduce to that in diploids except that the recombination is two thirds that for diploid genes the same distance apart, and the overall amount of selection acting is less than that for a diploid gene. The lowered recombination makes it easier to maintain a two-locus polymorphism with disequilibrium but the lowered amount of selection has the opposite effect. Overall it appears more difficult to maintain a two-locus polymorphism for haplodiploids or X-linked genes than for diploids (115). In addition, a certain level of epistasis is critical to maintain disequilibrium, an amount and type that probably is less likely to occur in haplodiploids or X-linked genes than in diploids.

Genetic hitchhiking may be more likely for haplodiploids or X-linked genes than for diploids, primarily because the overall rate of recombination is lower than in diploids. Theoretically this appears to be true, but Owen (115) has shown that for diploids without recombination in males, like *Drosophila*, the likelihood of hitchhiking is stronger than for haplodiploids or X-linked genes. In addition, haplodiploids or X-linked genes may have a smaller effective population size, which could generate disequilibrium, and a faster rate of change for favorable variants, which creates a better situation for genetic hitchhiking to occur (39, 71, 157).

Molecular data in *Drosophila* suggest that the amount of nucleotide variation varies greatly among genes and that there is generally a direct relationship between the level of recombination and the amount of variation observed (1, 5). Different regions of the X chromosome vary considerably in the amount of genetic variation and, for example, the telomeric region of the X chromosome in *D. melanogaster* has both low genetic variation and very low recombination (4). Currently two hypotheses, both based on genetic hitchhiking, seek to explain this association; they are termed selective sweeps (9) and background selection (22, 25). Briefly, the selective sweep hypothesis suggests that when an advantageous mutant arises and goes to fixation, it fixes neutral alleles in disequilbrium with it during the process. The background selection hypothesis suggests that detrimental alleles are spread over all chromosomes and are destined to be lost. When they decline in frequency, they reduce variation at neutral genes in disequilibrium with them. For both processes, the tighter the linkage, the larger the region influenced.

Mutation-Selection Balance and Inbreeding Depression

The input of mutations, which reduce fitness, and purifying selection, which eliminates these mutants, are thought to be two major factors influencing the frequency of detrimental or lethal alleles in a population. Because of the continuous exposure of detrimental or lethal alleles to selection in haploid males for haplodiploids and X-linked genes, it is generally assumed in a random-mating population that the frequency of detrimental alleles and the consequent genetic load would be lower than in diploids. If a population segregating for such fitness variation is inbred, the variants hidden as heterozygotes in a random-mating population are expressed, resulting in inbreeding depression. If there is less hidden variation, then the reduction in fitness upon inbreeding should be less, suggesting that inbreeding depression should be less in haplodiploids or X-linked genes than in diploids.

For example in random-mating diploids, the equilibrium frequency of a detrimental allele is $q_{e.d} = (u/s)^{1/2}$, and it is a function of the mutation rate (u) to this allele and of the amount of selection (s) against the allele, given that fitnesses of genotypes *AA*, *Aa*, and *aa* are 1, 1, and $1 - s$, respectively ($s = 1$ for lethals). For haplodiploids or X-linked genes, given that the fitnesses of male genotypes *A* and *a* are 1 and $1 - s$, respectively, then $q_{e.hd\text{-}X} = 3u/s$, a much lower level (59). To illustrate the difference, the ratio of these values is $q_{e.hd\text{-}X}/q_{e.d} = (9u/s)^{1/2}$, quite small for any reasonable values of s and u.

The equilibrium frequency of individuals with the lowered fitness is u/s for diploids. For haplodiploids or X-linked genes, this equilibrium is approximately $3u/2s$ in males and approaches zero in females, so the overall value, assuming an equal sex ratio, is $3u/4s$, or 25% lower than for diploids. In other words,

the expected genetic load is less for a detrimental allele in haplodiploids or X-linked genes than in diploids. These calculations make a number of assumptions, including that the allelic frequencies are the same in the two sexes, the detrimental allele is recessive, and selection is equivalent in both sexes.

Werren (166) relaxed these assumptions to determine, in general, the expected differences in genetic load between haplodiploids or X-linked genes and diploids. His theoretical conclusions were that in random-mating populations at equilibrium, the genetic load in haplodiploid or X-linked females is significantly lower than that in haploid males of a haplodiploid species or diploids, which generally have similar loads. For many parameter combinations, the genetic load for haplodiploids or X-linked genes is approximately 25% less than that of diploids (see 166, Figure 3.1), although the apportionment between sexes varies for different parameter combinations. In addition, for female-limited load, both the equilibrium allele frequency and genetic load are still lower for haplodiploids or X-linked genes than for female-limited diploids.

Inbreeding can take two general forms (166): chronic, as in a population that has a continuous level of inbreeding, or acute, as when a random-mating population undergoes a sudden high level of inbreeding (this, of course, occurs when the effect of inbreeding on fitness is determined experimentally). For chronic inbreeding, a new level of equilibrium genetic load is reached that is reduced more for diploids than for haplodiploids or X-linked genes. For acute inbreeding, the fitness is reduced in the first generations much more for diploids because the genetic load in a random-mating diploid population is higher.

Several types of data are relevant to these predictions about genetic load and inbreeding depression. First, the genetic load appears to be much less for the X chromosome than for the autosomes in *Drosophila*. For example, the median proportion of autosomal chromosomes in *D. melanogaster*, *D. pseudoobscura*, and *D. persimilis* that have a semilethal or lethal gene in natural populations is approximately 25% (45). In two samples of X chromosomes, the overall frequency of semilethal or lethal chromosomes was only 2.2% (47, 54), much less than for autosomes even when the smaller size of the X chromosome is taken into account. Overall, the total genetic load for viability (about half the load for the autosomal chromosomes is from detrimentals and half from lethals and semilethals) estimated for autosomes in *D. melanogaster*, *D. pseudoobscura*, and *D. willistoni* is 0.609 (151), and only 0.046 or less for the X chromosome in *D. melanogaster* (47)—a very large difference.

Second, the amount of genetic load in haplodiploids also appears to be less than that in the autosomes in the *Drosophila* studies, although, the number of studies are smaller. Lowered fitness or more bilateral asymmetry upon inbreeding in honey bees has been reported (14, 15, 83), but more recent studies have not found such effects (27, 28, 82). In studies on both *Drosophila* (46, 54, 84)

and honey bees (83), there is the suggestion that some of the observed viability load is limited to females. However, some of this effect may be artifactual (38) or due to lack of proper controls (47); the most extensive study of X-linked genetic load in *D. melanogaster* (47) showed no sex-limited genetic load for viability. On the other hand, the fitness reduction for X chromosomes observed in laboratory equilibrium experiments (167) may be the result of female-limited fertility effects.

Third, wild populations of *D. melanogaster* were surveyed in North Carolina and Great Britain for allozyme-null alleles, i.e., alleles that show no catalytic activity in their gel staining assay, at both autosomes and the X chromosome (90, 160). At 20 autosomal loci, 58 null alleles were found of 24,678 alleles screened, for an average frequency of 0.0024 (the North Carolina and British samples were quite similar). However, for these samples and a sample from Japan for five X-linked genes, no null alleles were found in 8,209 alleles screened, a highly significant difference. All but one of the null alleles were both viable and fertile (44). If these null alleles are assumed to be in mutation-selection equilibrium, the lower frequency of null alleles on the X chromosome than on the autosomes is consistent with theoretical predictions given above.

Neutrality

Under the neutrality theory, the amount of genetic variation is a function of the effective population size, variation being reduced through genetic drift, and mutation producing new variation. The expected heterozygosity for a diploid is $H_{e.d} = 4N_{e.d}u/(4N_{e.d}u + 1) = \theta_d/(\theta_d + 1)$, where u is the mutation rate to a new allele (87), the infinite-allele model. For a haplodiploid or X-linked gene, $H_{e.hd\text{-}X} = 4N_{e.hd\text{-}X}u/(4N_{e.hd\text{-}X}u + 1) = \theta_{hd\text{-}X}/(\theta_{hd\text{-}X} + 1)$ (108). Assuming a sex ratio of unity (and all other factors equivalent), $N_{e.hd\text{-}X} = 3N_{e.d}/4$, and $H_{e.hd\text{-}X} = 3N_{e.d}u/(3N_{e.d}u+1) = 0.75\theta_d/(0.75\theta_d+1)$ (98). For microsatellite loci, the stepwise-mutation model may be more appropriate (151, although see 50), and we will also give the ratio of θ values from the formula for the expected heterozygosity in this model, $H_e = 1 - 1/(1 + 8N_eu)^{1/2}$.

Similarly, the expectation at equilibrium of the amount of nucleotide diversity and the proportion of polymorphic sites for diploids is $\theta_d = \pi_d = 4N_{e.d}u$ (86) and for haplodiploids or X-linked genes is $\theta_{hd\text{-}X} = \pi_{hd\text{-}X} = 4N_{e.hd\text{-}X}u$. In this case, with a sex ratio of unity, $\theta_{hd\text{-}X} = \pi_{hd\text{-}X} = 3N_{e.d}u = 0.75\theta_d$ (104).

Avery (2) suggested that the observed variance of allozyme heterozygosity over species could be compared to its expectation under neutrality to determine if the pattern of allozyme variation is consistent with neutrality. This approach for both haplodiploid species within social categories (2) or haplodiploid species within genera (118) has shown good general agreement between the observed and theoretical variances, suggesting that the pattern of allozyme variation is consistent with neutrality.

There is some evidence that mutation rate in males is higher than that in females in primates (149) and rodents (19). If so, this results in a higher average mutation rate for autosomes than for X-linked genes because half of the genes are in males for an autosomal gene and only one third are for a X-linked gene. The average mutation rate for an autosomal (diploid) gene is $u_d = u_f/2 + u_m/2$ and that for a X-linked gene is $u_X = 2u_f/3 + u_m/3$. Assuming that the mutation rate in males is α times that in females, then $u_X/u_d = [2(2 + \alpha)]/[3(1 + \alpha)]$. As expected, this ratio is unity if there is no difference in mutation rate between the sexes and approaches two thirds as α becomes large (the estimates of α in primates and rodents are appproximately six and two, respectively). Using the expression above, when there is an equal sex ratio but assuming that $u_X = 2u_d/3$ then $H_{e.X} = 2N_{e.d}u_d/(2N_{e.d}u_d + 1)$ and $\theta_X = \pi_X = 2N_{e.d}u$, lowering the expected heterozygosity even further. Recently, there is the suggestion that mutation rates may be lower for X chromosomes than autosomes in rodents (99a), potentially resulting in a lower heterozygosity for X-linked than autosomal genes. Below we use estimates of heterozygosity and diversity to determine the difference in θ values for haplodiploids and diploids, and for X-linked and autosomal genes.

GENETIC VARIATION

Comparison of Haplodiploid and Diploid Insects

The earliest searches for allozyme variation in haplodiploids were largely unsuccessful (101, 133, 155). As a result, a variety of hypotheses, based primarily on evolutionary genetics, were invoked to explain this apparent lack of genetic variation. The most prominent explanation was that the expected effective population size for haplodiploids is three fourths that in diploids when there is an equal sex ratio, resulting in a proportionately lower heterozygosity in haplodiploids. There were also three hypotheses related to differences in selection between haplodiploids and diploids: The conditions for a stable polymorphism from selection were significantly more restrictive in haplodiploids so less variation would be maintained by selection in haplodiploids; allozyme alleles with a detrimental effect would have a lower equilibrium heterozygosity from mutation-selection balance for haplodiploids; and favorable variants, as they go to fixation, would be polymorphic for a shorter time in haplodiploids. Genetic hitchhiking has also been proposed as more important for haplodiploids than diploids, as mentioned above.

In addition, a number of studies have attempted to compare haplodiploids across levels of sociality (8, 34, 57, 87, 112, 131, 139, 140, 148). In general, eusocial haplodiploids were found to have reduced genetic variation relative to haplodiploids with a solitary life history. Several hypotheses were suggested

Table 1 Mean expected allozyme heterozygosity (*H*) and the standard error of the mean over species (in parentheses) for all studies and for studies with 15 or more loci divided by social category and species group for the given number of species

	All studies		≥15 loci		
Group	Species	*H*	Species	*H*	References
Haplodiploid insects	119	0.046 (0.004)	66	0.047 (0.005)	
I. Hymenoptera	115	0.046 (0.004)	6	0.046 (0.005)	
A. Eusocial	73	0.036 (0.004)	36	0.024 (0.004)	
1. Advanced	31	0.045 (0.006)	12	0.030 (0.006)	
a. Ants	26	0.041 (0.005)	10	0.036 (0.005)	8, 61, 132, 150, 164, 165
b. Bees	4	0.069 (0.041)	2	0.000	30, 162
c. Wasps	1	0.000	0		132
2. Primitive	42	0.031 (0.005)	24	0.021 (0.005)	
a. Bees	38	0.027 (0.005)	22	0.020 (0.006)	13, 88, 118, 121, 132, 140, 155, 160
b. Wasps	4	0.062 (0.010)	3	0.053 (0.005)	91
B. Social parasites					
a. Bees	5	0.010 (0.002)	2	0.008 (0.004)	118, 131, 132
C. Solitary	37	0.069 (0.009)	26	0.076 (0.008)	
a. Bees	10	0.035 (0.008)	3	0.057 (0.010)	91, 101, 131, 155
b. Wasps	13	0.065 (0.019)	9	0.051 (0.005)	20, 91, 100, 101, 131
c. Sawflies	14	0.096 (0.012)	14	0.096 (0.012)	11, 131, 148, 150
II. Thysanoptera					
A. Solitary	4	0.058 (0.011)	4	0.058 (0.011)	34
Diploid insects	151	0.117 (0.006)	151	0.117 (0.006)	
a. Drosophila	31	0.135 (0.060)	31	0.135 (0.060)	34, 57

to explain this association, including that selection in eusocial species from an environmentally constant nest was less likely to maintain genetic variation (131, 155), and that the effective population size in eusocial haplodiploids is smaller than that in solitary haplodiploids due to inbreeding (8).

In Table 1, we summarize data on allozyme variation from studies known to us. We divide the data into two categories: all studies, defined as those in which at least six loci were examined, and those in which ≥15 loci were examined (we also examined data for ≥20 loci, as suggested by 34, but the results were nearly identical to those for ≥15 loci). Some of these data are from earlier summaries, but we used the newer data if newer data on the same species were available. The expected heterozygosities (110) for each species were calculated and the unweighted mean and standard error were calculated over all species in a given category. The Hymenoptera were subdivided into categories based on

social status as suggested by 139, i.e. advanced eusocial (large perennial nests and sterile worker caste), primitive eusocial (small or annual nests, potentially fertile workers), and solitary. In addition, we separated the social parasites from the eusocial and solitary categories because they live in a eusocial environment but lack a worker caste.

Eusocial Hymenoptera demonstrate significantly lower heterozygosity compared to the solitary Hymenoptera, as found by others, both for all studies and for studies with $\geq$15 loci. However, the advanced eusocial species have somewhat higher heterozygosity than the primitive eusocial species, so the trend of higher heterozygosity in solitary species is not complemented with the lowest heterozygosity in advanced eusocial species. [A great part of the reason that the solitary species have a high mean heterozygosity is the high heterozygosity observed in sawflies.] Interestingly, the other haplodiploid insects for which there are data, four species of solitary Thysanoptera (thrips), have a heterozygosity similar to that of the hymenoptera.

Diploid insects have a higher heterozygosity than do haplodiploid insects, even when *Drosophila*, a group with high allozyme heterozygosity, is removed. The loci in diploid insects include those on all chromosomes, including the X, so that the expectation would be that if the X-linked loci were removed (the chromosomal location of the allozymes surveyed in most of these species is not known), the mean value would increase somewhat. However, heterozygosity levels at X-linked genes in *Drosophila* are similar to those for autosomal genes (2), and the diploid insect species with the largest sample of known X and autosomal loci, *D. melanogaster*, has a heterozygosity of 0.154 for both the 9 X-linked loci and the 54 autosomal loci examined (152).

If we use the mean heterozygosities of haplodiploids (0.047) and diploids (0.117) to estimate θ_{hd} and θ_d from the equations above, then $\theta_{hd}/\theta_d = 0.372$. This ratio is half that expected based only on the differences in effective population size, suggesting other differences between the two groups that result in lower heterozygosity in haplodiploids. Such factors in the haplodiploids could be a smaller overall effective population size, higher inbreeding, lower mutation rate, or some effect of sociality. Note that the inclusion of monomorphic loci reduces the expected difference between haplodiploids and diploids because these loci cannot decrease in heterozygosity further due to lower effective population size.

For the comparisons between groups to be more meaningful, it would be good to use the same number of homologous, polymorphic loci in two groups that differ only by a given characteristic. We know of no such related pairs of haplodiploids and diploids, but the eight species of naked mole rats show different levels of sociality (80). Eusocial, colonial, and solitary species have heterozygosities of 0.314 (one species), 0.215 (four species), and 0.281 (three

Table 2 Mean expected microsatellite heterozygosity (*H*) and the standard error over species (in parentheses) in haplodiploid insects and for microsatellites in *D. melanogaster*, with the mean number of loci per species

Group	Species	Loci	H	References
Haplodiploid insects				
A. Eusocial	12	5.2	0.459 (0.069)	
1. Advanced	4	4.0	0.700 (0.092)	
a. Ants	3	3.0	0.729 (0.092)	21, 52, 55
b. Bees	1	7	0.614	50
2. Primitive	8	5.4	0.338 (0.055)	
a. Bees	5	2.0	0.283 (0.080)	51
b. Wasps	3	12.3	0.340 (0.018)	26, 78, 156
Diploid insects				
a. Drosophila	1	81 (19*)	0.504 (0.715*)	49, 56, 102, 146, 147

*Dinucleotide microsatellite loci with 10 repeats or more.

species) respectively (80); the eusocial species had the highest heterozygosity, but the intermediate level of sociality, colonial, had the lowest.

Microsatellite loci, which are generally repeats of two, three, or four nucleotides, with different alleles at a locus having different numbers of repeats, have recently become the preferred type of polymorphic locus because they are codominant, often have high variability, and generally are consistent with neutrality. A summary of the studies to date of microsatellites in haplodiploid insects and *D. melanogaster* is given in Table 2. The lack of variability in allozyme loci that has plagued studies of social insects does not appear in microsatellite loci, as studies cited in Table 2 and others (62, 158) have found many variable loci. Because the mutation rate for microsatellite loci is generally higher than for allozyme loci, this finding is not unexpected.

In this preliminary summary of microsatellite variation in haplodiploids, the advanced eusocial species have a higher heterozygosity than do the primitive eusocial species, but the number of species and number of loci are quite small. The mean heterozygosity for all the haplodiploids (they are all eusocial here) is 0.459, somewhat lower than the mean of 0.504 for the 81 loci located to chromosome in *D. melanogaster*. Using these heterozygosity values, θ_{hd}/θ_d is 0.787 and 0.835 for the stepwise and infinite allele models. The amount of variation for many microsatellite loci in *D. melanogaster* is fairly low, possibly due to a low mutation rate (146), the small size number of repeats at many of these loci (147), and the location of many loci in this sample near transcribed genes. If the heterozygosity is calculated for the 19 known dinucleotide loci with more than ten repeats in *D. melanogaster* (as were nearly all the microsatellite loci

in the human and mouse studies discussed below), the average heterozygosity is much higher—0.715.

Comparison of X-Linked and Autosomal Genes

As mentioned above, the levels of heterozygosity for X-linked and autosomal allozyme loci in *D. melanogaster* appear similar (2, 152). A survey of RFLPs in humans showed about one third as much variation on X-linked as on autosomal markers (76), and a survey of nucleotide diversity for 49 human genes showed quite low variation overall (94), with some variation at two of the six X-linked loci and at 17 of the 46 autosomal loci. These studies have been superseded by extensive reports or summaries of X-linked and autosomal variation for nucleotide diversity (104) and microsatellites (147) in *D. melanogaster*, for nucleotide diversity in *D. simulans* (104), for marker polymorphisms [(89% were microsatellite loci and the remainder RFLPs) in the house mouse (42)], and for microsatellite loci in humans (43) (Table 3).

Nucleotide variation in *Drosophila* is evaluated in (104). It appears that excluding the loci in regions of low recombination differs little between X chromosomes and autosomes (104). However, the extensive data in mice and humans in Table 3 are part of the effort to map the genomes in these two species, so we briefly discuss some aspects of those data. The heterozygosities for the 216 microsatellite loci on the human X chromosome are given by location in Figure 4 (43, 53) along with the means for all 216 X-linked loci (0.65) and

Table 3 Variation at X-linked and autosomal loci and the ratio of θ_X/θ_A. "Number" for nucleotide diversity is the number of base pairs, and that for the other data is the number of loci. The amount of variation for nucleotide diversity and for the polymorphic loci in mice is θ, and that for the microsatellite loci is heterozygosity. The two values of θ_X/θ_A for microsatellite loci are for the stepwise and infinite allele models, respectively

	X-linked		Autosomal			
Species	Number	Variation	Number	Variation	θ_X/θ_A	References
Nucleotide diversity						
D. melanogaster	8,774	0.00274	14,757	0.00441	0.621	104
D. simulans	7,741	0.00470	7325	0.00971	0.484	104
Polymorphic loci						
M. musculus	230	0.330	6106	0.486	0.679	42
Microsatellite loci						
Humans	216	0.65	5048	0.70	0.708, 0.796	43
D. melanogaster	19	0.602	62	0.474	2.032, 1.679	49, 56, 102, 146, 147
	7*	0.670	12*	0.741	0.588, 0.710	

*Dinucleotide microsatellite loci with 10 repeats or more.

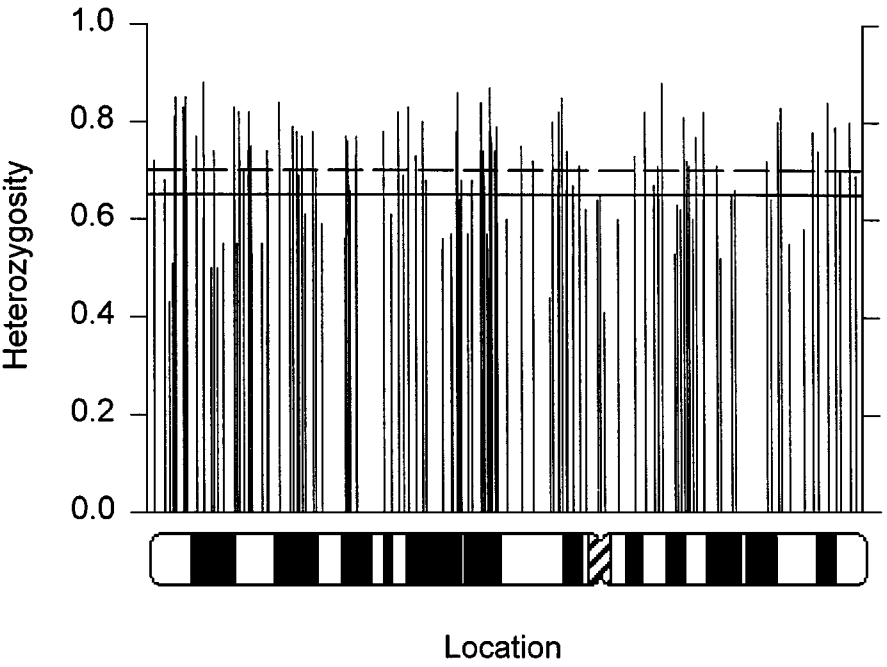

Figure 4 Heterozygosity for 216 microsatellite loci on the human X chromosome show by map location (adapted from 43, 53). The horizontal solid and broken lines indicate the mean heterozygosity for the X-linked genes and the 5048 autosomal genes, respectively.

all 5,048 autosomal loci (0.70). Notice that although there appears to be some clustering of variable sites along the chromosome, the loci near the ends of the chromosome do not appear to have significantly lower heterozygosity, as they do on the *D. melanogaster* X chromosome. This is not unexpected because recombination at the ends of the human X chromosome is not reduced. The range of heterozygosity over the 22 autosomes is fairly narrow, from 0.69 to 0.73, so that the heterozygosity for the X chromosome is significantly lower than that for autosomes. Similarly, the proportion of polymorphism for the 230 genes on the mouse X chromosome (0.33) was lower than that observed for any of the 19 autosomes (from 0.35 to 0.57). Neither of these studies are perfect population samples, with some of the variation in the mouse survey potentially coming from ancestry from *Mus domesticus* (42) and the human sample being composed of families, so that not all individuals are independent observations (43) (M Nachman, personal communication). However, these biases may not be too important, both because so many loci were studied and because we are interested in the amounts of variation for X-linked relative to autosomal genes.

The ratio of the estimated values in Table 3 of θ_X/θ_A are similar to, or slightly below, the 0.75 neutrality prediction for the difference in effective population size for all the comparisons, except in *D. simulans*, for which the X-linked nucleotide variation is only 0.484 that of the autosomal variation (see 104 for a discussion of this observation, and also 3). Particularly impressive is the fact that the variation at 6336 marker loci in mice and 5264 microsatellite loci in humans show ratios of 0.679 and 0.708 (stepwise) or 0.796 (infinite), values quite similar to the 0.75 value predicted under neutrality. These data do not appear consistent with the hypothesis that the primate mutation rate is higher in males than in females (or that the mutation rate is lower for X-linked than autosomal genes). If the male mutation rate was sixfold larger, then the predicted ratio for humans would be approximately 0.57, using the expression above, quite different from 0.708 or 0.796.

CONCLUSIONS

Evolutionary genetic theory predicts a number of differences between haplodiploids or X-linked genes and diploids. For example, the conditions for a polymorphism, the amount of genetic load, and the rate of change of new variants are all expected to be different. It is difficult to evaluate experimentally or empirically the differences between the two systems for the amount of selectively maintained polymorphism (there are few such documented polymorphisms for either system) or the rate of change of new variants. However, there does appear to be substantial experimental support for lower genetic load and inbreeding depression for X-linked than for autosomal genes and some support for less inbreeding depression in haplodiploids than diploids.

For neutral molecular variation, the expected effective population size is smaller for haplodiploids or X-linked genes than for diploids and should result in less genetic variation. For comparisons of allozymes between haplodiploids and diploids, and for comparisons between X-linked variants and autosomes for nucleotide diversity in *Drosophila*, and for microsatellites in mice, humans, and *D. melanogaster* (for dinucleotide repeats of 10 or more), the observations are quite consistent with these predictions. However, we caution that such consistency does not necessarily mean that we have the correct explanation for these observations. There are several discrepancies, i.e., the level of variation for haplodiploids relative to diploids and the variation for X-linked to autosomal genes in *D. simulans* are even less than predicted by theory. As we have mentioned, other differences, such as a smaller overall effective population size for haplodiploids than for diploids, or an indirect effect of sociality on effective population size or level of inbreeding, could contribute to the difference between haplodiploids and diploids.

Several observations suggest that loci may have quite varied properties. First, and as often noted, the allozyme loci sampled vary greatly between species and may include loci with different levels of variability or different proportions of polymorphic loci, factors that could dilute any predicted differences. Second, in *Drosophila*, the amount of variation at a given locus appears to be directly correlated with the level of recombination in that region, suggesting that more detailed linkage information would be preferable for the markers used in such comparisons. Third, the amount of variation for microsatellite loci appears to be a function of the size of the repeat, the number of repeats, and probably, for some unknown reason at this point, the species examined (147).

Finally, researchers interested in the population genetics of haplodiploids and those working on X-linked genes are generally two quite separate groups. Obviously, knowledge of the population genetics for these two very similar systems is significant and sophisticated. We hope that we have succeeded here in demonstrating the usefulness of population genetics theory and data from haplodiploids for application to X-linked genes and for X-linked genes to haplodiploids.

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