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Model for evolution of Y chromosomes and dosage compensation

(sex chromosomes/mutation)

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ABSTRACT **Some difficulties with the classical model for the evolution of a genetically inert Y chromosome are discussed. An alternative model is proposed, which is based on the principle of Muller's ratchet; this involves the accumulation of chromosomes bearing deleterious mutant genes in a finite population in the absence of crossing-over. This process would result in the gradual increase, with time, in the number of mutant loci carried in an average Y chromosome, although the frequency of individual deleterious alleles at most loci remains low. It is shown that this creates a selection pressure for differentially increasing the activity of the X chromosome in heterogametic individuals at the expense of that of the Y, leading eventually to a genetically inert Y chromosome and to the evolution of dosage compensation.**

The Y chromosome of many species either does not cross-over at all with the X chromosome or is divided into two parts, one of which crosses over (the pairing segment) and the other of which does not cross-over (the differential segment) (1). Genetic and cytological observations suggest that the Y chromosome as a whole in the first case or the differential segment in the second is largely devoid of genetic function. The commonly accepted explanation for this is due to Muller (2, 3). He assumed that the initial state of the sex chromosomes was such that the X and Y chromosomes contained the same complement of genes but that they failed to cross-over with each other, either wholly or in a part of the chromosome. Muller proposed that a chromosome or chromosome region that is kept permanently heterozygous, without being able to cross-over with its homologue, will tend to accumulate recessive lethal or deleterious mutations; such mutations are effectively neutral because they can never become homozygous. Recurrent mutation from wild-type to recessive alleles that causes the loss of the function of a locus is thus unopposed by selection, so that there is a gradual increase in the frequency of mutant alleles, eventually resulting in the loss of the wild-type allele at the locus concerned. Over a sufficiently long period of evolutionary time, therefore, the Y chromosome, or its differential segment, becomes fixed for recessive, loss-of-function alleles at most of its loci.

This theory was criticized by Fisher (4) on the following grounds. He noted that the primeval X chromosome is also exposed to recurrent mutation to deleterious alleles, at a rate comparable to that for the Y chromosome. This results in selection against a Y mutant whenever the individual carrying it also contains a deleterious, allelic mutant gene on the X chromosome. Fisher showed that the frequency of recessive lethal mutants in an infinite population is the same for both X and Y loci, unless the mutation rate is much higher for the Y. Nei (5) has reinvestigated this question and shown that the effect of random drift in a finite population can result in a somewhat higher rate of chance fixation of deleterious recessive mutant alleles for a Y locus. His calculations show, however, that this effect is very small unless the effective population size is less than about 10,000 or the mutations concerned are nearly neutral. The effective population size that is relevant for calculating rates of chance fixation of genes is that for the whole species, not the local population (6), and so it would seem unlikely that this process could play an important role in most species. Furthermore, studies of spontaneous mutations in *Drosophila melanogaster* by Mukai and others (7, 8) have shown that mildly deleterious mutations are, on average, far from being recessive. Lethal mutations, which seem to come closest to recessivity, show an average reduction in viability of about 4% when heterozygous. This makes it extremely unlikely that deleterious mutations with other than very mild effects could be fixed as a result of mutation and drift in a small population. The probability of fixation of a deleterious, semidominant mutation is largely determined by its effect when heterozygous with wild-type (6). Hence, the rate of chance fixation of mildly deleterious mutations at loci on the Y chromosome is unlikely to be significantly higher than for an autosomal locus.

Finally, if the genetic inertness of the Y chromosome is due to the accumulation of recessive, loss-of-function alleles, it is difficult to understand why the phenomenon of dosage compensation (9–11) should have evolved. This ensures that the single X chromosome of XY individuals produces the same amount of gene product as the two X chromosomes in an XX individual. On Muller's theory, one gene dose at a locus is assumed to be as fit as two, so that there would be no selective pressure in favor of dosage compensation. Muller himself pointed out that dosage compensation suggests that most mutations are not recessive in their effects on fitness (12).

Muller's ratchet and the Y chromosome

For the above reasons, it seemed desirable to seek alternatives to Muller's theory of the evolution of a genetically inert Y chromosome. The hypothesis proposed here is based on a process originally suggested by Muller as a mechanism for the evolution of genetic recombination (13) and named "Muller's ratchet" by Felsenstein (14). The properties of this process have recently been studied theoretically (15–17) and will be outlined briefly here. Consider first a chromosome of a discrete-generation haploid organism in which there is no recombination and which is liable to mutations to deleterious alleles at each locus. In a finite population, with time there will be a gradual increase in the number of mutant loci per chromosome, even though at most loci the wild-type allele is kept at a high frequency by

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natural selection. To understand how this occurs, consider first what happens in an effectively infinite population. Let the number of mutations that occur per generation on an individual chromosome follow a Poisson distribution with mean u. (Each mutation is assumed to occur at a unique site; back-mutation, which is usually much less frequent than forward mutation, is ignored.) If the mutant alleles are subject to selection in such a way that the fitness of an individual decreases with the number of mutant loci that it carries, the population eventually comes to an equilibrium in which the rate of input of new mutant genes into the population is balanced by the selective elimination of carriers. This equilibrium population is characterized by the frequency distribution of chromosomes carrying, 0, 1, 2, . . . , etc. mutant loci. For example, let the selection coefficient against an individual mutant gene be s, and assume that gene effects combine multiplicatively across loci. The fitness of an individual carrying i mutant loci is thus $(1 - s)^i$. At equilibrium, the number of mutant loci per chromosome then follows a Poisson distribution with mean u/s (16, 17), so that the number of individuals with no mutant loci is $n_0 = N \exp(-u/s)$, in which N is the population size.

If we now assume that the population is large but finite and if n_0 is sufficiently small, the mutant-free class of chromosomes is vulnerable to loss by random drift. Because no recombination takes place, once the mutant-free class has been lost in this way, it cannot be regenerated by crossovers between chromosomes carrying different sets of mutant loci, so that Muller's ratchet has moved one step, irreversibly. The class of chromosomes carrying only one mutant locus now plays the same role as the mutant-free class, and is eventually irreversibly lost in the same way, giving another turn of the ratchet. The population eventually attains a steady rate of movement of the ratchet, which is largely determined by the value of n_0 (16). This causes a continual increase in the mean number of mutant loci per chromosome.

The main features of this process can be applied to the primeval Y chromosome or its differential segment. I assume, with Muller (2, 3), that the Y chromosome is initially active and homologous with the X but fails to cross over with it. The relevant population size N is now the total number of Y chromosomes in the population (i.e., half the number of individuals), and the mutation rate u is that for the primeval Y or its differential segment, which can reasonably be assumed to have the same value as that for the corresponding region of the X chromosome. The selection coefficient s is now the net selection coefficient against a Y chromosome mutant in an XY individual. The only complicating factor is the occurrence of mutations at allelic loci on the X chromosome; this has the consequence that a Y mutation will have a low frequency of exposure to selection in the homozygous state (4), thus slightly increasing the value of s over what it would be for a mutation heterozygous with wild-type. In principle, therefore, a genetically active Y chromosome is exposed to the action of Muller's ratchet, owing to its unique permanent heterozygosity.

At present it is uncertain whether or not mutation rates, selection coefficients, and population sizes are such that the ratchet is likely to produce a significant accumulation of deleterious mutations on Y chromosomes in a natural population. This uncertainty arises partly from the difficulty of obtaining precise theoretical estimates of the rate of operation of the ratchet in a large population (16, 17) and partly from our ignorance of the values of the parameters involved. As far as the latter are concerned, the most relevant data are provided by the work of Mukai and his associates (7, 8) on the spontaneous mutation of the second chromosome of *D. melanogaster*. This work yields a *minimum* estimate of u of about 0.11 for mildly deleterious mutations affecting egg-to-adult viability and a *maximum* estimate of 0.02 for s. Taking into account the fact that the X chromosome has about one-half of the amount of genetic material of the second chromosome and that the average heterozygous effect of a mutant viability allele is about 35% of its homozygous effect (8), we obtain a minimum estimate of u/s for the primeval Y chromosome of 7.8 for mutations affecting viability. Haigh's figure 1 (16) shows that the ratchet produces a change from about 9 to 17 in the mean number of mutant loci per chromosome, over a period of 1000 generations, assuming a population size of 10^5 and with $u = 0.2$, $s = 0.02$.

The estimates of u and s from the *Drosophila* experiments therefore are consistent with the operation of the ratchet at an evolutionarily significant rate in a fairly large population. It should be remembered, however, that no information is available about the values of u and s for loci affecting fertility, although recent evidence suggests that fertility may well be at least as important a component of fitness as viability in *Drosophila* (8). Taking fertility mutations into account could affect our view of the likely importance of the ratchet in either direction. Furthermore, our ignorance of the value, in nature, of the effective population size relevant to the ratchet is almost total, particularly because the consequences of population subdivision and restricted migration have not been studied theoretically. However, present data are not inconsistent with the idea that Muller's ratchet may produce a gradual increase, over evolutionary time, in the number of mutant genes carried by a primeval Y chromosome. It should be noted that the frequency of mutant alleles at most loci is expected to be small, under this theory, in contrast with Muller's classical model for the evolution of the Y chromosome (2, 3). Some random fixation of mutant alleles must occur, but it is at present uncertain what influence the ratchet has on the rate of such fixation events.

Evolution of an inert Y chromosome and dosage compensation

The application of this model to the evolution of a genetically inert Y chromosome, and the associated phenomenon of dosage compensation, is straightforward. If we consider a stage of evolution in which the ratchet has proceeded some way, most of the Y chromosomes in the population will carry a number of loci with impaired function. There is clearly a selective advantage to genes that in some way enhance the rate of transcription of X chromosome loci in males in such a population, relative to the rate for Y loci. This requires that the number of mutant loci on an average Y be sufficiently large to outweigh any disadvantage due to the increased expression of mutant loci on the X. The details of the ways in which this process is likely to be accomplished will vary from one species to another. I shall outline below some hypotheses relating to Y chromosome evolution and the evolution of dosage compensation in three groups of organisms.

Drosophila. Evidence concerning the molecular basis of dosage compensation in *Drosophila* is consistent with either of two somewhat different evolutionary pathways. First, there could initially be selection for increased transcription specifically from the X chromosome, so that the defective products of the mutant loci on the Y chromosome are to some extent compensated for. After this has happened, selection would favor devices that reduce transcription from the Y, with a consequent saving of resources and restoration of the proper balance of gene activity between the sex chromosomes and the autosomes. Alternatively, one could imagine a situation in which there is a limited supply of some regulatory molecule or molecules needed for transcription of the X and Y chromosomes. If, in some way, the Y chromosome were made at least partially unresponsive to the regulatory molecules, an increased

supply could become available to the X in a male, raising its rate of transcription at the expense of that of the Y.

In both of these models, the evolution of a genetically inert Y chromosome is an active process rather than just an accumulation of nonfunctional genes and is accompanied by the evolution of dosage compensation. The end result is a largely inert Y chromosome and a male X that is transcribed at twice the rate of a female X (except for loci involved in sex determination). Both models require that inactivation of the Y chromosome and enhancement of the X chromosome in males must be nonspecific with respect to which loci are affected. This is because the selective advantage of both these phenomena is due to the fact that the Y chromosome of each individual carries a number of mutant genes, but the actual loci involved vary from individual to individual. It is of course possible that different segments of the sex chromosomes may evolve at different rates, provided that each segment of the Y is sufficiently large that it comes to contain a selectively significant mean number of mutant loci as the ratchet proceeds.

Once a genetically inert Y chromosome has been evolved by this pathway, selection will be ineffective against loss of Y fragments or even of the whole Y chromosome (if it carries no male fertility factors). There could even be a selective advantage to this, because energy needed for Y chromosome replication would be saved. The way is therefore open for morphological differentiation of the X and Y chromosomes, as is observed in many groups of organisms (1).

Current knowledge of the molecular basis of dosage compensation in *Drosophila* is consistent with either of these models. It is known that the X chromosome of a male is transcribed at about twice the rate of one of the X chromosomes in a female (10, 18). This could have evolved as a result of an *increase* in the rate of transcription of the male X chromosome compared with its original state, as postulated here, or because of the establishment of genes that *decrease* the activity of the female X chromosomes. The latter process appears to be envisaged in Muller's theory of dosage compensation (19), which postulates the existence of sex-linked "compensator" genes that turn the female X chromosome down. However, there is evidence from a number of *Drosophila* species that the X chromosome in the salivary glands of a male is approximately twice as wide as an autosome or an X chromosome in a female, suggesting that the male X chromosome has been raised in activity (20). This conclusion is supported by evidence from species of *Drosophila* in which new sex chromosomes have been produced as a result of a centric fusion between the ancestral X or Y and an autosome.

For example, the X of *D. pseudoobscura* has resulted from a fusion between the ancestral X and an autosome homologous with 3L of *D. melanogaster*. Similarly, the Y of *D. miranda* has resulted from a fusion between the ancestral Y and an autosome homologous with chromosome 3 of the closely related *D. pseudoobscura*. This produces a sex chromosome system with two X chromosomes, one of which (X^1) is homologous with the ancestral X and the other (X^2) with the ancestral autosome. In the case of *D. pseudoobscura*, dosage compensation appears to be complete for the autosomally derived arm of the X (21, 22). In the case of *D. miranda*, dosage compensation has been demonstrated at the level of transcription for part of the X^2 chromosome but is absent from the distal 10% (23). This agrees with genetic and cytological evidence for partial genetic activity of the Y (24). As pointed out by Lucchesi (25), it is difficult to understand how dosage compensation could evolve in these systems if it involved a reduction in the activity of the new female X chromosome or chromosome arm, because this would imply a disturbance of the balance between the products of the genes concerned and the products of other loci. No such disturbance occurs on the hypothesis of a reduction in the gene activity of the new Y chromosome or chromosome arm, accompanied by an increase in the activity of the homologous X chromosome genes in the male. There is, in addition, some direct evidence for an increased activity of the male X, from comparisons between transcription rates of sex chromosomes and autosomes (25).

Mammals. The ratchet hypothesis can also be applied to the evolution of dosage compensation in mammals, in which one of the two X chromosomes in the female is largely inactive in transcription (11). In marsupials, it is always the paternal X chromosome that is inactivated (26, 27); in eutherian mammals, inactivation of either the paternal or the maternal X chromosome of a cell occurs at random within a cell line (11). The same net level of gene activity of X-linked loci results, in males and females, in both these cases. It has been suggested that the eutherian system of X chromosome inactivation has evolved from the marsupial type of mechanism (28, 29). This could have the following selective advantage. In the marsupial system, all the somatic cells of a female will be hemizygous for any deleterious gene of maternal origin; with the eutherian system, only half the cells will be hemizygous for such a gene (29). Furthermore, the X chromosome inherited from the male is expected to contain a smaller number of deleterious genes than the maternal X chromosome, owing to its having been exposed to selection in the hemizygous condition in the previous generation. Therefore, there is an advantage in allowing it to express itself. Although there are grounds (11) for doubting the detailed models of dosage compensation proposed in refs. 28 and 29, it is nevertheless attractive to suppose that the eutherian system has evolved from a marsupial system. [This idea is consistent with embryological evidence for a monophyletic origin of eutherians and marsupials (30).] For purposes of further discussion, I shall assume that this is in fact the case and shall confine myself to the origin of the marsupial system.

Suppose that the primeval mammalian Y chromosome was genetically active and homologous with the X chromosome but failed to cross over with it, at least in a substantial differential segment. As discussed above, there would be selection for increased transcription of the X chromosome in males, once Muller's ratchet had moved to a significant extent. If for some reason the genes causing this increased rate of transcription were not sex-limited in effect, there would also be increased transcription of the X chromosomes in females. As in *Drosophila*, selection for conservation of resources in males and restoration of the sex chromosome/autosome balance could lead to the evolution of an inert Y chromosome (except for sex-determining genes and genes in the pairing segment). Similarly, selection in females would favor the restoration of X chromosome activity to its original level. As has been suggested by several authors (11, 29), paternal X inactivation could easily have evolved by exploiting the inactivation of the X chromosome in male germ cells from the primary spermatocyte stage onward, which has been observed in many species (31). If the change in state of the X chromosome occurring in spermatocytes were in some way to become transmissible to the resulting female zygotes, this would have the selective advantage noted above and would result in paternal X inactivation.

Plants. The evolution of the Y chromosome by Muller's ratchet may help to explain certain observations on sex ratios in flowering plants. In some dioecious species, X-bearing pollen grains seem to show competitive superiority over Y-bearing pollen, at any rate in conditions of heavy pollen competition on stigmas. This results in a sex ratio among seedlings that is biased in favor of females and has been interpreted as due to the genetic erosion of the Y chromosome and thus reduction of

the performance of male gametophytes (32). It is difficult to understand this on Muller's original theory (2, 3), because one would expect deleterious genes that express themselves in the pollen to be kept rare by selection. The ratchet model, however, predicts that chromosomes that carry several deleterious genes affecting pollen will eventually be established, provided that there is a sufficiently large number of loci controlling pollen function on the primeval Y chromosome. (The rate of movement of the ratchet might well be lower for such genes, because they are exposed to more intense selection than are genes that do not affect the pollen.) Furthermore, if there is sufficiently strong selection for reducing the activity of the Y chromosome or its differential segment, on the lines discussed above for *Drosophila* and mammals, this might lead to Y chromosomes that do not function efficiently in the pollen. It may be significant in this respect that poor performance of Y-bearing pollen has been observed only in plants with morphologically differentiated Y chromosomes (32).

A rather different outcome is predicted by the ratchet model for dioecious plants in which sex determination occurs in the haploid gametophyte phase of the life cycle—e.g., in Bryophytes. Here the male and female gametophytes contain Y and X chromosomes, respectively, and the diploid sporophytes are always XY in constitution. Any consequences of restricted crossing-over between the sex chromosomes thus apply equally to the X and Y (33, 34). Muller's ratchet will thus operate for the differential segments of *both* sex chromosomes and would be expected to bring about a gradual accumulation of deleterious mutations. There is, however, no selection pressure for increasing the activity of the X at the expense of the Y (or vice versa) and hence no selection for genetic erosion of either sex chromosome. The same is true on the classical model for the erosion of the Y (34). There is indeed some evidence that the sex chromosomes of Bryophytes are both genetically active, despite the existence of morphological differences between them in some species (34, 35).

Discussion

The model of the evolution of a genetically inert Y chromosome and of dosage compensation through Muller's ratchet is, at least, a serious alternative to Muller's classical hypothesis (2, 3). It is difficult to think of empirical tests that could distinguish between these models. The main evidence in favor of the ratchet model is that it is free from several of the objections to the classical model, as discussed above. The ratchet model would be made highly implausible if the existence of compensator genes of the type suggested by Muller (19) were demonstrated in *Drosophila*. At present, the balance of evidence seems to be against compensator genes. In the first place, there is the evidence that dosage compensation in *Drosophila* evolves by an increase in the activity of the male X chromosome rather than by a decrease in the activity of the female X chromosomes (20, 25). Second, the experiments of Stewart and Merriam (36) on the effects of small X chromosome duplications failed to demonstrate the existence of compensator genes. Their results are broadly consistent with the hypothesis that dosage compensation in *Drosophila* is due to limitation of the rate of X chromosome transcription by regulatory molecules present at the same concentration in males and females (37, 38). If this hypothesis were confirmed, it would be consistent with the second of the two models proposed above for the evolution of dosage compensation in *Drosophila*. Of course, none of these facts constitutes decisive evidence in favor of the ratchet model.

It is perhaps worth pointing out that, although this model predicts that dosage compensation is nonspecific with respect to which loci are affected, in the sense that compensation mechanisms have not evolved separately for each X chromosome locus, it is quite possible for some X loci to be more or less fully compensated than others. For instance, some loci might happen to have regulatory sites that are insensitive to the regulatory molecule or molecules involved in increasing the activity of the other genes on the X. This could account for the existence of apparently uncompensated genes in *D. melanogaster* (19) and *D. miranda* (23).

Another alternative to the classical model of the genetic erosion of the Y chromosome has been suggested by Hamilton (39). In a species that has an element causing meiotic drive of the primeval Y chromosome (at the expense of the X) in XY individuals, there is selection in favor of autosomal or X-linked genes that suppress the drive, by Fisher's principle of selection for a 1:1 sex ratio (40). One way of achieving this suppression is simply to inactivate the Y chromosome. Provided that the loss of fitness caused by suppressing the gene products of the Y is outweighed by the advantage of readjustment of the sex ratio, this process could certainly operate. But it is difficult to understand why inactivation of such a large amount of genetic material is necessary when, in other systems of meiotic drive, specific suppressors of the drive have been evolved (41); such suppressors would not suffer the disadvantage of turning off an entire chromosome or chromosome region. In addition, it is increasingly clear that meiotic drive systems are due to genes of highly specialized effects (41) and it is difficult to believe that every species with an inert Y chromosome has had a history of meiotic drive on the Y.

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