# The Evolution of Sex Chromosomes

BRIAN CHARLESWORTH

**Structurally distinct sex chromosomes (X and Y) are the most familiar mode of genetic sex determination and have evolved independently in many different taxa. The evolutionary paths by which their characteristic properties may have evolved are reviewed. These properties include the failure of X and Y to recombine through much or all of their length, the genetic inertness of much of the Y chromosome, dosage compensation of the activity of X chromosomal loci, and the accumulation of repeated DNA sequences on the Y chromosome.**

SEXUAL REPRODUCTION WITH SOME DEGREE OF GAMETE dimorphism is nearly universal among eukaryotes (*1*). Male and female gametes may be produced by the same individual (cosexuality) or by separate individuals (dioecy or gonochory). Most terrestrial animal species are dioecious, but cosexuality is widespread among marine invertebrates and land plants (*1*). Mechanisms of sex determination are astonishingly diverse (*2*). The most familiar form of genetic sex determination involves structurally distinct sex chromosomes. The commonest condition is male heterogamety, in which males carry X and Y sex chromosomes and females are XX (Fig. 1). With female heterogamety, females are ZW and males are ZZ (for brevity only X and Y chromosomes are referred to from now on, but most of what follows applies equally to Z and W). Characteristically, there is little or no recombinational exchange between X and Y chromosomes. In some taxa, recombination is suppressed over part of the sex chromosomes as a result of chromosomal inversions distinguishing X and Y; in others, exchange is limited to a small region of the XY pair (as in mammals), and sometimes crossing over in all chromosomes is restricted to the heterogametic sex (as in *Drosophila* and Lepidoptera) (*2–5*).

The absence of genetic exchange is associated with a lack of genetic homology between the relevant regions of the X and Y chromosomes. In mammals, the pairing region at one end of the Y contains loci homologous with loci on the X, whereas the rest of the chromosome largely lacks functional loci apart from a small number required for male sex determination and fertility (*2–5*). In *D. melanogaster,* the Y is largely devoid of functional genetic loci other than a cluster of ribosomal RNA genes, six loci required for male fertility, and the *Stellate* locus (*4*). Much of the Y seems to consist of highly repeated DNA sequences similar in nature to transposable elements and to satellite sequences of the type associated with centric heterochromatin, and indeed the Y is usually described as heterochromatic (*2, 4, 6,* 7). In many species, it is variable in size (*3, 8*), suggesting that these sequences are of no functional significance.

Dosage compensation is a corollary of the lack of functional loci on the Y and the resulting hemizygosity of the X in the heterogametic sex. This phenomenon involves adjustment of the activity of X-linked loci such that the rate of transcription in males is effectively twice that in females. In eutherian mammals, this is achieved by inactivation of one of the pair of X chromosomes in females, whereas in *Drosophila* and *Caenorhabditis elegans* it is achieved by greater transcription of X chromosomal loci in males (*2, 9*).

There are numerous examples of intermediate levels of structural and genetic differentiation between X and Y chromosomes (*2–4, 10*). It is therefore probable that advanced systems originated from ones in which the X and Y were initially largely homologous genetically. The parallel evolution of advanced sex chromosome systems in different groups (*2–4*) strongly suggests that relatively simple evolutionary forces have been involved. The problem of identifying these forces has long attracted the attention of geneticists. The classic explanation of the genetic inactivity of the Y chromosome is attributable to Muller, who assumed that X and Y were originally homologous but lacked genetic exchange through all or part of their length (*11*). He suggested that a chromosome region that is maintained permanently heterozygous without exchange with its homolog will accumulate deleterious recessive mutations, because their increase under mutation pressure will not be resisted by selection. Fisher (*12*) pointed out that this mechanism is unworkable because the proto-X contains the same loci as the proto-Y, so that recessive Y-linked mutations will encounter allelic mutations carried on the X and be subject to elimination by selection. In addition, this theory does not explain dosage compensation because there would be no need to compensate for the loss of Y chromosomal gene activity if mutational effects were completely recessive (*13*). Early theorizing often did not specify in detail the processes by which the population as a whole came to acquire the properties in question (*14*). Recent theoretical work, coupled with advances in empirical knowledge of the genetics and evolution of sex-determining systems, has provided a richer understanding of the possible paths by which the features of advanced sex-determining systems have evolved.

## Evolution of Separate Sexes and Primitive Sex Chromosomes

Although the remote ancestors of many present-day taxa with separate sexes may have been cosexual, the evolutionary history of sex determination usually cannot be traced back to this source (*2*). In the case of flowering plants, however, the recent origin of dioecy from a cosexual state is often clear (*10, 15*). Such cases provide a useful testing ground for models of the evolution of dioecy. At least two mutational steps are required to evolve dioecy from cosexuality: a male sterility mutation converting cosexuals into females, and a female sterility mutation converting cosexuals into males (Fig. 2A). The first step in the evolution of dioecy is likely to involve the invasion of the cosexual population by females, establishing a

The author is in the Department of Ecology and Evolution, University of Chicago, Chicago, IL 60637.

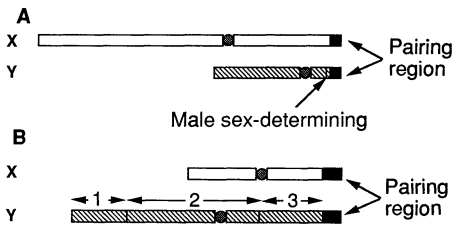


**Fig. 1.** (**A**) Diagram of the general structure of the human X and Y chromosomes (*5*). The filled circles represent the centromeres. The unshaded region of the X contains active genes that are absent from the hatched region of the Y, with which it does not undergo recombinational exchange. The filled regions at the ends of the short arms of the X and Y undergo pairing and genetic exchange. The male-determining genes of the Y are located just to the left of the pairing region. (**B**) The structure of the X and Y chromosomes of the red campion *Silene dioica* (*10*). Region 1 of the Y carries a gene or genes suppressing femaleness, region 2 promotes maleness, and region 3 promotes anther development. The clear region of the X promotes femaleness and does not cross over with the Y.

polymorphism for females and cosexuals (gynodioecy). The second phase involves the conversion of the cosexuals into males, either by a single female sterility mutation or by a more gradual series of stepwise reductions in female fertility (*16*).

Two major causal factors drive this process: resource reallocation and avoidance of inbreeding (*1, 15, 16*). The first involves the idea that a mutation reducing male or female fertility may cause an increase in the fertility of the opposite sex function as a result of the reallocation of resources devoted to reproduction. The second involves the fact that an individual with only one sex function cannot self-fertilize, so that its progeny will escape the loss in fitness often associated with close inbreeding. If this effect is important in the evolution of dioecy, the original cosexual population must experience a significant level of self-fertilization; this is supported by comparative evidence indicating that the close relatives of dioecious plant species are usually self-fertile (*17*).

The first step toward dioecy is more likely to involve a male sterility mutation than a female sterility mutation because the access of male gametes to the female gametes of other plants is restricted by self-fertilization. This reduces the genetic value of maleness relative to femaleness in a self-fertile, cosexual population (*16*). Furthermore, a mutation reducing male fertility is more likely to be favored if it has a large effect because small effects will rarely reduce the rate of self-fertilization significantly. Once females are present in the population, there is a greater advantage to maleness than in the initial state, and mutations reducing female fertility, and concomitantly increasing male fertility, can spread. There is no special selective premium on mutations of large effect at this stage, so that multiple loci with small effects on female fertility may be involved (*16*). Individuals that combine both male and female sterility genes have a net loss in fitness, so that the second phase is most likely to occur if the female sterility mutations occur at loci that are tightly linked to the male sterility locus (Fig. 2B). In addition, there is selection for genes or chromosome rearrangements restricting crossing over between the loci controlling male and female sex phenotype and for modifiers of dominance that create complementary dominance relations between the two kinds of sterility genes. Otherwise, intermediate sex phenotypes will be present in the population (subdioecy) (*16*). Given the probable complete loss of male fertility in the initial step, subdioecious populations should show intergradation between males and cosexuals, with females forming a distinct class, as is indeed observed (*10, 15, 16*).

With full dioecy, a primitive sex chromosome system must have been established. The proto-X will carry genes conferring female fertility and male sterility, and the proto-Y will confer female sterility and male fertility (Fig. 1B). Genetic analyses of cases of genetic sex determination without obvious structural differences between X and Y indicate that this system is common in species in which dioecy evolved recently (*10*). If the initial male sterility mutations are most often recessive, male heterogamety will be commoner than female heterogamety (Fig. 2B). Because recessivity is characteristic of loss of function mutations, and because advantageous recessive alleles can readily become established in partially inbreeding populations, this probably explains the relative frequencies of these two types of sex determination (*2, 16*).

This simple model thus explains a wide variety of facts. It suggests that the first step in the evolution of sex chromosomes involves restriction of recombination between genes controlling male and female sex function rather than throughout all or most of the X and Y chromosomes. Primitive sex chromosome systems often show this pattern (*2, 10*). Why then should more extensive restriction of genetic exchange often evolve? Any genetic variant that is advantageous in the heterogametic sex but strongly disadvantageous in the homogametic sex will spread through the population only if it is linked to the sex-determining region of the Y chromosome (*18*). Examples of this are provided by the bright color patterns of male fish such as *Poecilia* and *Xiphophorus* (*2*). Despite their higher vulnerability to predation, these patterns are advantageous to males through sexual selection (*19*). Restriction of recombination between the sex-determining region and loci controlling such secondary sexual characteristics will be favored by selection (*2*). The elaboration of physiologic, morphologic, and behavioral differences between the sexes leads to selection for further allelic differences between the proto-X and proto-Y and to reduced genetic exchange over a wide region.

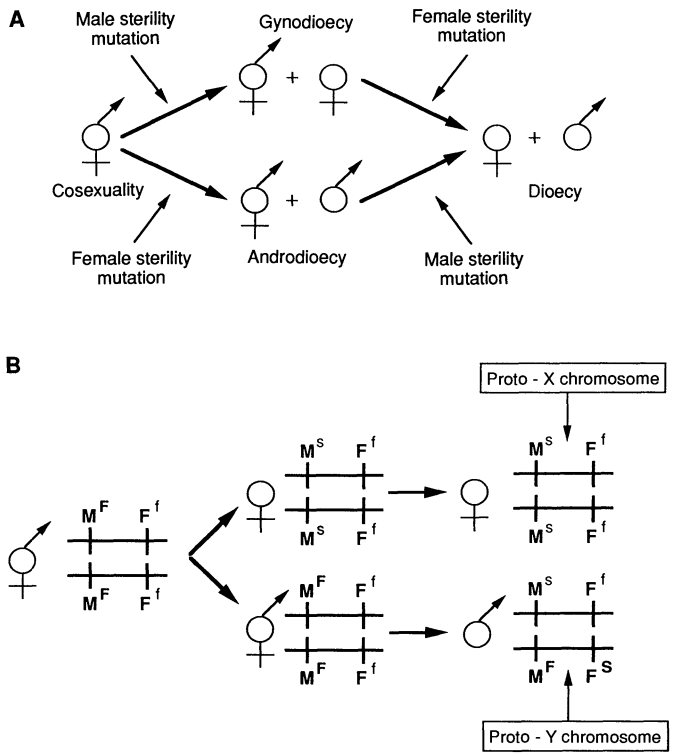


**Fig 2.** (**A**) The minimum number of mutational steps needed to produce dioecy. If a male sterility mutation arises first, a polymorphism for cosexuals and females (gynodioecy) is established. If a female sterility mutation arises first, a polymorphism for cosexuals and males (androdioecy) is established. Gynodioecy is not uncommon, but androdioecy is virtually unknown, as is predicted theoretically (*16*). (**B**) The evolution of proto–sex chromosomes, assuming an initial recessive male sterility mutation ($M^F \rightarrow M^s$) and a subsequent dominant female sterility mutation ($F^f \rightarrow F^S$) at a closely linked locus.

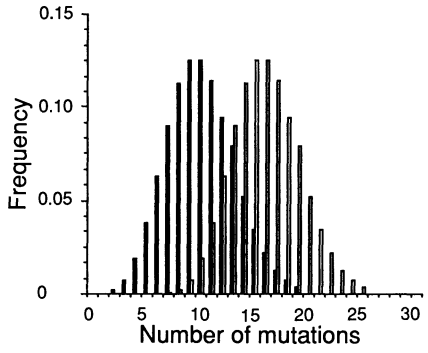


**Fig. 3.** The operation of Muller's ratchet on a nonrecombining genome. The filled bars illustrate the equilibrium distribution of numbers of mutant loci per individual for a model of a haploid genome with a mutation rate of 0.2 per genome per generation and a selection coefficient of 0.02 against a mutation at a given locus. The open bars represent the distribution after 600 generations in a population of $10^5$ individuals (*22*).

## Evolution of a Degenerate Y Chromosome and Dosage Compensation

The above steps lead to the stage postulated by Muller in his classic explanation of the degeneration of the Y chromosome (*11*). As discussed above this explanation is untenable, but several alternatives have been proposed (*13, 20, 21*). The two most mechanistically feasible alternatives are as follows. One invokes the stochastic process known as Muller's ratchet (*13*). Consider a chromosomal region containing a large number of loci susceptible to deleterious mutations (Fig. 3). Mutant alleles at each locus are kept at a low frequency by selection. In an infinite population, an equilibrium distribution of the number of mutant loci per individual is set up. If there is no recombination in this region, and if back-mutations are rare, the class with no mutations may be lost from the population and cannot be restored. Next, the class carrying just one mutation also becomes vulnerable to chance loss, and so on. As time progresses, the mean number of mutations per chromosome steadily increases without fixation of deleterious alleles at the loci concerned (*1, 22*).

The operation of Muller's ratchet on a proto-Y chromosome creates selection in favor of increasing the activity of the X relative to the Y in the heterogametic sex (except for genes controlling sex expression and loci in the pairing region). Reducing transcription from the Y while increasing transcription from the X in the heterogametic sex would cause a *Drosophila* type of dosage compensation to evolve in concert with the inactivation of the Y. If the increase in X activity were not limited to the heterogametic sex then an inactive Y would evolve, but without dosage compensation, as may be the case in birds and Lepidoptera (*2*). A mammalian type of dosage compensation could have evolved as a response to this kind of situation because it creates a selective advantage to reducing X activity in the homogametic sex, thereby restoring the balance between autosomal and X chromosomal gene products. The endpoint of this would be total inactivation of the X in the homogametic sex, as is now observed in eutherian mammals. Paternal X inactivation, which is found in marsupials, may be an intermediate stage in this process (*13*).

The second process (*21*) depends on the fact that, in the absence of recombination, the spread of a favorable Y-linked mutant allele through a population causes fixation of deleterious alleles at other loci that happen to be present in the Y chromosome in which the mutation originated (hitchhiking). There will then be selection for increased activity of the homologous loci on the X chromosome of the heterogametic sex, leading to stepwise reduction of the Y's activity and increased activity of the X as successive favorable Y-linked mutations become fixed.

## Accumulation of Repeated DNA Sequences on the Y Chromosome

Transposable elements, which can self-replicate and insert into new sites, are expected to accumulate on the Y chromosome for several reasons. Once the genetic activity of the Y has been reduced, there will be fewer deleterious fitness consequences of insertions into the Y, and hence transpositional increase in element abundance will not be opposed by selection (*23*). Furthermore, recombination between similar sequences at different sites generates deleterious chromosome rearrangements and eliminates the elements concerned. In the absence of exchange this cannot happen, so that elements will tend to accumulate (*23*). Finally, accumulation of elements may occur by Muller's ratchet in regions where exchange is absent (*23*).

Tandem repeats of simple DNA sequences (without transpositional capabilities) are also expected to accumulate in regions of restricted exchange (*24*). Unequal exchange between repeated sequences causes no change in the mean number of repeats but increases the variance. In a finite population, and in the absence of all other evolutionary forces, chance fixation of a chromosome carrying one copy of the sequence will eventually occur, and the population will remain trapped in this state. Loss of a family of repeats is thus promoted by unequal exchange. If there is weak selection against individuals carrying large numbers of repeats but repeats are generated occasionally by an amplification process, then the mean number of repeats equilibrates at a much higher level if exchange is infrequent (*24*). The accumulation of both simple sequences and transposable elements on the Y chromosomes is thus part of a broader pattern, whereby such sequences are expected to accumulate in regions of restricted genetic exchange. There is empirical evidence for this pattern (*4, 6, 7, 23, 24*).

## Conclusions

Evolutionary explanations of the major features of sex chromosome systems, based firmly on population genetic principles, are now available. Some of these, such as the evolution of separate sexes and primitive sex chromosomes in plants, are supported by a good deal of genetic and comparative evidence. Some alternative pathways to dioecy and sex chromosomes are also well supported by models and data, such as the evolution of dioecy from distyly in plants (*25*) and the transitions between different modes of genetic sex determination in animals (*2*).

Other aspects are less well established. For example, genetic sex determination in vertebrates may sometimes have evolved from environmental sex determination rather than from cosexuality (*2*), but detailed genetic evidence on the nature of this transition is lacking. Similarly, sex determination in *Drosophila* and *C. elegans* involves a balance between female-determining genes on the X and male-determining autosomal factors (*9*), whereas the model described here is for male-determining genes on the Y. A scenario can be developed to explain X-autosome balance systems without greatly changing the outlines of the above processes (*26*), but this is wholly speculative at present. There are also no data that discriminate between the Muller's ratchet and hitchhiking explanations of the degeneration of the Y chromosome and dosage compensation (which are not strict alternatives, both being processes that must almost inevitably occur).

To make progress toward answering some of these questions, more evidence is needed on the comparative genetics and molecular biology of sex-determination systems, particularly for primitive sex chromosome systems of recent origin. Such studies may shed light

on questions such as whether degeneration and dosage compensation usually evolve on a stepwise, gene-by-gene basis (*21*) or involve large blocks of chromosomal material (*13*). Secondary sex chromosomes, in which neo-X and neo-Y chromosomes have been created by centric fusions between old-established sex chromosomes and autosomes, are also a rich potential source of new facts (*27*).


REFERENCES AND NOTES

1. J. M. Smith, *The Evolution of Sex* (Cambridge Univ. Press, Cambridge, 1978).
2. J. J. Bull, *Evolution of Sex Determining Mechanisms* (Benjamin Cummings, Menlo Park, CA, 1983).
3. M. J. D. White, *Animal Cytology and Evolution* (Cambridge Univ. Press, Cambridge, 1973).
4. B. John, in *Heterochromatin: Molecular and Structural Aspects,* R. S. Verma, Ed. (Cambridge Univ. Press, Cambridge, 1988), pp. 1–147.
5. N. A. Ellis and P. N. Goodfellow, *Trends Genet.* **5**, 406 (1989).
6. A. Lohe and P. Roberts, in *Heterochromatin: Molecular and Structural Aspects,* R. S. Verma, Ed. (Cambridge Univ. Press, Cambridge, 1988), pp. 148–186.
7. E. M. Eicher, K. W. Hutchison, S. J. Phillips, P. K. Tucker, B. K. Lee, *Genetics* **122**, 181 (1989).
8. T. Dobzhansky, *ibid.* **20**, 366 (1935).
9. J. C. Lucchesi, *Science* **202**, 711 (1978); J. Hodgkin, *Nature (London)* **344**, 721 (1990).
10. M. Westergaard, *Adv. Genet.* **9**, 217 (1958).
11. H. J. Muller, *Genetics* **3**, 422 (1918).
12. R. A. Fisher, *Am. Nat.* **69**, 446 (1935).
13. B. Charlesworth, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 5618 (1978).
14. C. D. Darlington, *Evolution of Genetic Systems* (Oliver & Boyd, Edinburgh, 1958).
15. C. R. Darwin, *The Different Forms of Flowers on Plants of the Same Species* (John Murray, London, 1877).
16. D. Charlesworth and B. Charlesworth, *Proc. R. Soc. London Ser. B.* **205**, 513 (1979); *Evolution* **41**, 948 (1987).
17. D. Charlesworth, in *Evolution: Essays in Honour of John Maynard Smith,* P. J. Greenwood, P. H. Harvey, M. Slatkin, Eds. (Cambridge Univ. Press, Cambridge, 1985), pp. 237–269.
18. R. A. Fisher, *Biol. Rev.* **6**, 345 (1931); W. R. Rice, *Evolution* **41**, 911 (1987).
19. J. A. Endler, in *Predator–Prey Relationships,* M. E. Feder and G. V. Lauder, Eds. (Univ. of Chicago Press, Chicago, 1986), pp. 109–134.
20. W. D. Hamilton, *Science* **156**, 477 (1967); M. Nei, *Am. Nat.* **104**, 311 (1970).
21. W. R. Rice, *Genetics* **116**, 161 (1987).
22. H. J. Muller, *Mutat. Res.* **1**, 2 (1964); J. Haigh, *Theor. Popul. Biol.* **14**, 251 (1978).
23. B. Charlesworth and C. H. Langley, *Annu. Rev. Genet.* **23**, 251 (1989).
24. ———, W. Stephan, *Genetics* **112**, 359 (1986); W. Stephan, *Mol. Biol. Evol.* **6**, 198 (1989).
25. D. G. Lloyd, *Plant Syst. Evol.* **131**, 71 (1979); B. B. Casper and E. L. Charnov, *J. Theor. Biol.* **96**, 143 (1982); D. Charlesworth, *ibid.* **139**, 327 (1989).
26. B. Charlesworth, in preparation.
27. E. Strobel, C. Pelling, N. Arnheim, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 931 (1978); M. Steinemann, *Chromosoma* **89**, 59 (1982).


28. I thank D. Charlesworth, C. Langley, and W. Stephan for their collaborations on many of the ideas reviewed here; J. Bull for comments on the manuscript; and the National Science Foundation and the National Institutes of Health for supporting some of the research reviewed here.


# Physics in Strong Magnetic Fields Near Neutron Stars


ALICE K. HARDING



**Electromagnetic phenomena occurring in the strong magnetic fields of neutron stars are currently of great interest in high-energy astrophysics. Observations of rotation rate changes and cyclotron lines in pulsars and γ-ray bursts indicate that surface magnetic fields of neutron stars often exceed $10^{12}$ gauss. In fields this strong, where electrons behave much as if they were in bound atomic states, familiar processes undergo profound changes, and exotic processes become important. Strong magnetic fields affect the physics in several fundamental ways: Energies perpendicular to the field are quantized, transverse momentum is not conserved, and electron-positron spin is important. Neutron stars therefore provide a unique laboratory for the study of physics in extremely high fields that cannot be generated on Earth.**


PHYSICAL CONDITIONS INFERRED TO EXIST IN ASTROPHYSICAL sources are often far outside the realm of conditions now achievable in laboratories on Earth. The highest magnetic fields in Earth-bound experiments, generated by implosive flux-compression (*1*), are in the tens of megagauss. Some white dwarf stars have fields that are about 10 times higher. The discovery of radio pulsars and then of x-ray binaries and γ-ray bursts revealed that neutron stars have fields that are a million times higher ($10^{12}$ G), possibly the highest fields occurring in nature. In teragauss magnetic fields the cyclotron energy approaches the electron rest mass, and quantum effects become important. Many neutron stars emit radiation at x-ray and γ-ray energies, requiring acceleration of particles to at least tens of megaelectron volts. The combination of relativistic particle energies and quantizing magnetic fields requires a quantum electrodynamic (QED) description of the physical processes. By observing the radiation emitted by neutron stars, we can study the physical processes that are thought to occur only in these extremely high magnetic fields. This article reviews some of the theoretical work on the physics in strong magnetic fields as well as what observations of neutron stars can tell us about the behavior of radiative processes under these extreme conditions.


The author is an astrophysicist at the Laboratory for High Energy Astrophysics, National Aeronautics and Space Administration, Goddard Space Flight Center, Greenbelt, MD 20771.


## Neutron Star Magnetic Fields

There are presently two ways to measure neutron star magnetic fields, and both independently indicate field strengths exceeding $10^{12}$ G. The first method involves monitoring neutron star rotation periods and determining their rate of change. The periods of radio pulsars are observed to increase with time. It is now widely accepted that these isolated neutron stars can be modeled as rotating magnetic dipoles emitting electromagnetic dipole radiation that creates a torque, causing them to spin down in a well-determined way. Because this torque is related to the star's magnetic dipole moment