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Aberrant Chromosomal Sex-Determining Mechanisms in Mammals, with Special Reference to Species with XY Females [and Discussion]

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Aberrant chromosomal sex-determining mechanisms in mammals, with special reference to species with XY females

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Both mouse and man have the common XX/XY sex chromosome mechanism. The X chromosome is of original size (5–6 % of female haploid set) and the Y is one of the smallest chromosomes of the complement. But there are species, belonging to a variety of orders, with composite sex chromosomes and multiple sex chromosome systems: XX/XY_1Y_2 and $X_1X_1X_2X_2/X_1X_2Y$. The original X or the Y, respectively, have been translocated on to an autosome. The sex chromosomes of these species segregate regularly at meiosis; two kinds of sperm and one kind of egg are produced and the sex ratio is the normal 1:1. Individuals with deviating sex chromosome constitutions (XXY, XYY, XO or XXX) have been found in at least 16 mammalian species other than man. The phenotypic manifestations of these deviating constitutions are briefly discussed. In the dog, pig, goat and mouse exceptional XX males and in the horse XY females attract attention. Certain rodents have complicated mechanisms for sex determination: *Ellobius lutescens* and *Tokudaia osimensis* have XO males and females. Both sexes of *Microtus oregoni* are gonosomic mosaics (male OY/XY, female XX/XO). The wood lemming, *Myopus schisticolor*, the collared lemming, *Dicrostonyx torquatus*, and perhaps also one or two species of the genus *Akodon* have XX and XY females and XY males. The XX, X* X and X* Y females of *Myopus* and *Dicrostonyx* are discussed in some detail. The wood lemming has proved to be a favourable natural model for studies in sex determination, because a large variety of sex chromosome aneuploids are born relatively frequently. The dosage model for sex determination is not supported by the wood lemming data. For male development, genes on both the X and the Y chromosomes are necessary.

INTRODUCTION

There are more than 4000 living species of mammal in the world. Like man and the mouse, the great majority have XX and XY sex chromosomes, but there are exceptions to the rule. In this paper I briefly discuss those exceptions, and also point out how exceptional individuals, and species with aberrant sex chromosome mechanisms, may contribute to our understanding of sex determination.

MULTIPLE SEX CHROMOSOME SYSTEMS

Apparently complex sex chromosome systems can occur by translocations between one of the sex chromosomes and an autosome (Fredga 1970). When the original X has been translocated on to an autosome the sex chromosome mechanism is designated $XX(♀)/XY_1Y_2(♂)$ (or A^XA^X/A^XYA). The Y_1 is the original Y chromosome and Y_2 is the homologous autosome to which X was translocated. Thus Y_2 has nothing to do with sex determination. In species of this group the male has one chromosome more than the female. The long-nosed rat-kangaroo (*Potorous tridactylus*), the common shrew (*Sorex araneus*) and the Indian muntjac (*Muntiacus muntjak*) are the best-known examples of this group.

When the Y has been translocated on to an autosome the sex chromosome mechanism is

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designated $X_1X_1X_2X_2$(♀)/X_1X_2Y(♂) (or XXAA/XAA^Y). The X_1 is the original X chromosome and X_2 is the homologous autosome to which the Y was translocated. In species of this group the female has one chromosome more than the male. Mongooses of the genus *Herpestes* and spiral-horned antelopes of the genus *Tragelaphus* belong to this group.

Sometimes both the X and the Y fuse with the homologues of an autosome pair. Then large sex chromosomes occur which form a distinct chiasma (or chiasmata) at male meiosis. Male and female have the same chromosome number. The Chinese hamster (*Cricetulus griseus*) is a well-known example of this group.

However, all these species with composite sex chromosomes are from the point of view of sex determination rather unexciting. The sex chromosomes are distributed regularly at male meiosis and two kinds of sperm and one kind of egg are produced.

INDIVIDUALS WITH DEVIATING SEX CHROMOSOME CONSTITUTIONS IN SPECIES WITH NORMAL SEX CHROMOSOMES

There are individuals with deviating sex chromosome constitutions in several mammalian species as well as in man. Table 1 lists these species, both wild and domesticated. Only the commonest types of deviation are included, and mosaics are excluded unless no other example of that particular type of sex chromosome aberration has been reported. This applies particularly to the XYY group. Occasional mosaic specimens have been reported in the common shrew (XY/XYY), the cat (XY/XXY/XXYY; XX/XY/XXY/XXYY), the horse (XO/XYY), and cattle (XY/XYY). (References are given in table 1; in each row with more than one sex chromosome type, the references are given from left to right.) I shall not describe in detail the individual chromosome deviations and their phenotypic manifestations in the various species and specimens listed, but only give some general comments. Reviews of this field are given by Gustavsson (1980), Benirschke (1981) and Rieck & Herzog (1984).

The sex chromosome aneuploids considered here are those most commonly found in man. The incidence of XXY and XYY is approximately 1 per 1000 among newborn males, as is the incidence of XXX among females, but XO individuals make up only 2 per 10000 newborn females (Bond & Chandley 1983).

Thus it is not surprising that XXY individuals have been reported in several (10) of the 16 species listed in table 1. In addition, XXY wood lemmings have been found (table 3). It is remarkable that 'pure' XYY and XXX are so rare, only found in two species each: for example, no XXX mouse has been reported so far. The XO constitution, on the other hand, is relatively common and has been found in 11 of the species listed. It is also found in the wood lemming where it is the commonest sex chromosome deviation; among 220 wild-captured wood lemmings 6 were XO (Fredga *et al.* 1989).

The XXY constitution gives the same phenotypic manifestation in all species: they have a male phenotype in terms of external appearance and accessory reproductive structures, but are infertile due to testicular hypoplasia.

The XO constitution always gives a female phenotype, but there is a remarkable difference between large and small species with regard to fertility. Large mammals (with a long generation time) are infertile, small mammals are fertile. The rhesus monkey, the horse and the sheep have gonadal dysgenesis as in man. The XO tammar wallaby and XO pigs are infertile intersexes. In cattle only one single XO heifer has been reported; it had low-grade ovarian hypoplasia with follicles. The fertility of the few XO cats reported is as yet unknown.

In small rodents like the black rat, the mouse and the wood lemming, XO females are fertile, but at least in the mouse the reproductive lifespan is reduced owing to premature exhaustion of the supply of oocytes. The important difference between XO mice and XO women may simply be one of timescale, XO mice reaching puberty before X-deficiency effects in the oocyte become severe, XO women reaching puberty after all oocytes have degenerated (Lyon & Hawker 1973; Burgoyne & Biggers 1976).

In table 1 several species are also listed as having individuals with the 'wrong' chromosome constitution in relation to phenotypic sex. XX male individuals have been reported in the dog, pig, goat and mouse: they all have different genetic causes for the discrepancies between sex chromosome constitution and phenotypic sex.

Table 1. Exceptional individuals in normal XX/XY mammal species (mosaics in brackets)

	phenotype						
	male			female			
species	XXY	XYY	XX	XO	XXX	XY	references[a]
tammar wallaby, *Macropus eugenii*	x	·	·	x	·	·	1
common shrew, *Sorex araneus*	x	(x)	·	·	·	·	2–3
rhesus monkey, *Macaca mulatta*	·	·	·	x	·	·	4
dog, *Canis familiaris*	x	·	x	·	·	·	5–6
cat, *Felis catus*	x	(x)	·	x	·	·	7–9
horse, *Equus caballus*	(x)	(x)	·	x	x	x	10–14
pig, *Sus scrofa*	x	·	x	x	·	·	15–17
cattle, *Bos taurus*	x	(x)	·	x	x	·	18–25
goat, *Capra hircus*	·	·	x	·	·	·	26–27
sheep, *Ovis aries*	x	·	·	x	·	·	28–29
South American field mouse, *Akodon azarae*	·	·	·	x	·	·	30
Chinese hamster, *Cricetulus griseus*	x	·	·	·	·	·	31
mole rat, *Bandicota bengalensis*	·	·	·	x	·	·	32
black rat, *Rattus rattus*	x	·	·	x	·	·	33–35
brown rat, *Rattus norvegicus*	·	x	·	·	·	·	36
mouse, *Mus musculus*	x	x	x	x	·	x	37–45

[a] 1, Sharman *et al.* (1970); 2, Searle (1984); 3, Searle & Wilkinson (1986); 4, Weiss *et al.* (1973); 5, Clough *et al.* (1970); 6, Selden *et al.* (1978); 7, Centerwall & Benirschke (1973); 8, Loughman & Frye (1974); 9, Norby *et al.* (1974); 10, Chandley *et al.* (1975); 11, Höhn *et al.* (1980); 12, Kent *et al.* (1986); 13, Kent *et al.* (1988); 14, Trommershausen Bowling *et al.* (1987); 15, Breeuwsma (1968); 16, Breeuwsma (1970); 17, Nes (1968); 18, Scott & Gregory (1965); 19, Rieck (1970); 20, Dobryanov & Konstantinov (1970); 21, Handa & Muramatsu (1981); 22, Miyake *et al.* (1984); 23, Refsdal (1979); 24, Rieck *et al.* (1970); 25, Norberg *et al.* (1976); 26, Hamerton *et al.* (1969); 27, Soller *et al.* (1969); 28, Bruère *et al.* (1969); 29, Zartman *et al.* (1981); 30, Bianchi & Contreras (1967); 31, Ivett *et al.* (1978); 32, Sharma & Raman (1971); 33, Yong (1971); 34, Yosida *et al.* (1974); 35, Satya Prakash & Aswathanarayana (1977); 36, Yosida (1984); 37, Russell & Chu (1961); 38, Cattanach (1961); 39, Cattanach & Pollard (1969); 40, Rathenberg & Müller (1973); 41, Evans *et al.* (1978); 42, Das & Kar (1981); 43, Lyon *et al.* (1981); 44, Welshons & Russell (1959); 45, Eicher (1982).

In the dog intersexes are relatively common in cocker spaniels (Hare 1976). Selden *et al.* (1978) have described in some detail a family of cockers including an XX male with unilateral cryptorchidism (right inguinal testicle), hypoplastic penis, hypospadias and a uterus. The mother of this dog was an XX phenotypic female, but in fact she was a true hermaphrodite with bilateral ovotestes containing prominent testicular tubules as well as mature ovarian follicles. One possibility is that part of the Y (*Tdy*) had translocated on to one of the X chromosomes, and that the variable expression in mother and son was due to non-random inactivation of one or the other X chromosome (X or X^{y}).

The XX pigs included in table 1 are male pseudohermaphrodites, and so are the XX goats.

In the goat, sex reversal is closely associated with a dominant autosomal gene for hornlessness (Polled). All genetic females that are homozygous for Polled develop as phenotypic intersexes with testes and ovotestes.

The mouse XX males are the well-known XX^{Sxr} individuals. Sex reversal is explained by the translocation of a male-determining gene (*Tdy*) from the Y to one of the X chromosomes. XX^{Sxr} mice are phenotypically normal but sterile males.

The XY females in horses are of particular interest, because the XY sex-reversal syndrome is characterized by both genotypic and phenotypic heterogeneity. The gene(s) responsible for the syndrome can be transmitted through a carrier female or male. Pedigree analyses suggest two modes of inheritance: (i) an autosomal sex-limited dominant or an X-linked recessive transmitted though the female, and (ii) an autosomal sex-limited dominant or a Y-chromosomal mutation with variable expression transmitted though the male (Kent *et al.* 1986). The carrier stallion produced both XY daughters and normal XY sons, but no XX sons were found, as would be expected if this stallion had an increased probability of transferring a male-determining gene from his Y to his X at meiosis.

The phenotypic spectrum of the XY females ranges from nearly normal females to greatly masculinized mares. Kent *et al.* (1988) identified four phenotypic classes in 38 XY mares: (1) nearly normal female, of which two were fertile (5 mares); (2) female with gonadal dysgenesis, normal mullerian development (14 mares); (3) intersex mare with gonadal dysgenesis, abnormal mullerian development, enlarged clitoris (15 mares); and (4) virilized intersex characterized by high levels of testosterone (4 mares). The transmission of the XY sex-reversal syndrome probably involves at least two genes: a primary sex-reversing gene, and a modifier gene or group of genes (Kent *et al.* 1988).

SPECIES WITH ABERRANT SEX-CHROMOSOME MECHANISMS

Several species, all rodents, have aberrant sex-chromosome mechanisms (table 2). Two species, the collared lemming (*Dicrostonyx torquatus*) and the wood lemming (*Myopus schisticolor*) are well known because they have XY females. They will be dealt with in some detail below.

The next species in this group is the creeping vole (*Microtus oregoni*), famous for being a gonosomic mosaic in both the male (YO/XY) and the female (XX/XO) (table 2).

TABLE 2. SPECIES WITH ABERRANT SEX-CHROMOSOME MECHANISMS

	sex chromosomes				
	female		male		
	soma	germ	soma	germ	references[a]
Dicrostonyx torquatus	XX, X*X, X*Y	XX, X*X, X*Y	XY	XY	1–4
Myopus schisticolor	XX, X*X, X*Y	XX, X*X, X*X*	XY	XY	5–9
Microtus oregoni	XO	XX	XY	YO	10–12
Ellobius lutescens	XO	XO(?)	XO	XO	13–23
Tokudaia osimensis	XO	?	XO	XO	24–25

[a] 1, Gileva & Chebotar (1979); 2, Gileva (1980); 3, Gileva *et al.* (1982); 4, Gileva (1983); 5, Fredga *et al.* (1976); 6, Gropp *et al.* (1976); 7, Fredga *et al.* (1977); 8, Herbst *et al.* (1978); 9, Schempp *et al.* (1985); 10, Matthey (1958); 11, Ohno *et al.* (1963); 12, Ohno *et al.* (1966); 13, Matthey (1953); 14, Matthey (1964); 15, Castro-Sierra & Wolf (1967); 16, Schmid (1967); 17, Castro-Sierra & Wolf (1968); 18, Maza & Sawyer (1976); 19, Nagai & Ohno (1977); 20, Wolf *et al.* (1979); 21, Vorontsov *et al.* (1980); 22, Djalali *et al.* (1986); 23, Vogel *et al.* (1988); 24, Honda *et al.* (1977); 25, Honda *et al.* (1978).

Two species, the mole-vole (*Ellobius lutescens*) and the Amami spinous country rat (*Tokudaia osimensis osimensis*), have XO males and females without any visible difference in the karyotype of the two sexes. The smallest chromosome, no. 9, in *Ellobius lutescens* has long been presumed to be the X. This has recently been proved by Vogel *et al.* (1988). Still to be proven is whether or not a Y-chromosome-specific DNA sequence (*Tdy*) has been translocated to the X of males. Males express serological H-Y antigen; females do not (Nagai & Ohno 1977). It has been suggested that heteromorphism of autosome pair no. 1 might be associated with sex determination (Maza & Sawyer 1976; Wolf *et al.* 1979), but this does not seem to be so (Djalali *et al.* 1986).

The sex chromosomes of these species have puzzled scientists for a long time and their mode of sex determination is still a matter of debate. A critical review, with special emphasis on evolutionary aspects, was given by Fredga (1983).

Species with suspected XY females

In addition to *Dicrostonyx* and *Myopus* a few other rodent species may have XY females. Five species of South American field mice of the genus *Akodon* are characterized by variation in the size and shape of the X chromosome, and by the fact that some females have sex chromosomes indistinguishable from those of the male. *A. mollis* is perhaps the strongest candidate among the field mice to have XY females. In this species the Y chromosome has a morphology and G-band pattern similar to that shown by the short arm of the X, though the latter exhibits a pericentromeric C-band that is missing in the Y chromosome. Because the Y-like chromosome in heteromorphic females also lacks a C-band, these females were assumed to be XY (Lobato *et al.* 1982).

In the four other *Akodon* species, *A. azarae* (Bianchi & Contreras 1967; Bianchi *et al.* 1976), *A. varius* and *A. boliviensis* (Bianchi *et al.* 1971) and *A. puer* (= *A. coenosus*) (Vitullo *et al.* 1986), the Y chromosome of the male and the Y-like chromosome of some females are also morphologically indistinguishable. However, the very small size of these C-band-positive sex chromosomes makes a detailed comparison impossible. The Y-like chromosome of the females has usually been interpreted as an X with an extensive deletion of the long arm. Breeding experiments with females of the two main chromosome types, XX and Xx(XY?) in *Akodon azarae* did not conclusively solve the problem (Lizzarralde *et al.* 1982), but in my opinion the data presented may well be interpreted in favour of the XY hypothesis; *Akodon* would then be comparable to *Dicrostonyx*. However, in contrast to the situation in *Dicrostonyx* and *Myopus* there are no reports of a skewed sex ratio in favour of females in natural populations of any of the *Akodon* species.

In *Nesokia indica* the X and the Y chromosomes show a great variation in size and morphology (Jhanwar & Rao 1973; Kamali 1975; Rao *et al.* 1983). Because the karyotypes of some females are indistinguishable, in unbanded preparations, from those of the predominating type of male (Kamali 1975), the possibility that XY females might exist in this species was put forward (Fredga 1983). However, C-staining of the chromosomes of *Nesokia indica* from Delhi, India, showed that the variation in size and morphology of the sex chromosomes was due to differences in the amount and distribution of constitutive heterochromatin (Rao *et al.* 1983; I. Nanda 1987, personal communication). Thus 'true' XY females probably do not exist in *Nesokia*.

A situation similar to that of *Nesokia indica* has also been reported for *Bandicota bengalensis*

bengalensis (Sharma & Raman 1973), namely variation in size of the sex chromosomes due to addition or deletion of constitutive heterochromatin.

A comparison of the sex chromosomes in two lemming species with XY females

In the collared lemming (*Dicrostonyx torquatus*) and in the wood lemming (*Myopus schisticolor*) the mechanisms of sex determination are similar. Three sex-chromosome types of female exist, namely XX, X* X and X* Y. Males are XY. The asterisk designates an X-linked mutation that affects the interaction of sex-determining genes, thus converting X* Y individuals into females. The two types of X chromosome, X and X*, in *Myopus* are distinguishable by the G-band patterns of their short arms (Herbst *et al.* 1978). The short arm of the X* is about 7% shorter than that of the X, and this size difference corresponds to approximately 1000 kilobases of DNA. The presumed origin of the variant X* chromosome is demonstrated in figure 1.

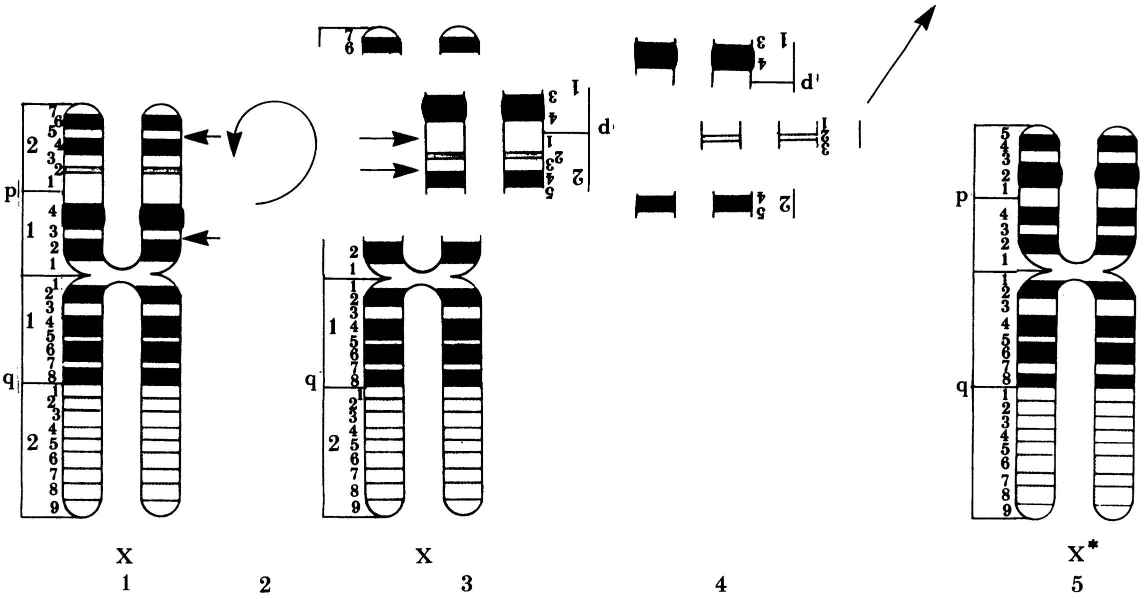

FIGURE 1. Presumed origin of the variant X chromosome (X*) in the wood lemming. 1. Two breaks in positions p13 and p25. 2. Inversion of this segment. 3. Two breaks in position p21 and p23. 4. Loss of this segment, including the tiny band p22. 5. Reunion of broken ends.

The Y chromosome of wood lemmings in Scandinavia is of intermediate size (relative length 5.7 of female haploid set) and is metacentric (centromeric index 41.2). It is a heterochromatic chromosome, easily recognized after C- or G-banding. There is no difference between the Y of XY males and X* Y females (Fredga *et al.* 1976). In geographically more eastern areas the centromere of the Y is more terminally located (Finland: K. Fredga, unpublished observation; U.S.S.R.: Gileva *et al.* (1983); Kozlovsky (1985)). All populations of *Myopus* studied have X* Y females and apparently the same kind of sex-determining mechanism.

In contrast to *Myopus*, the two types of X in *Dicrostonyx torquatus* cannot be distinguished cytologically. In addition, no easily distinguishable Y chromosome is present. The chromosome constitution in the various races and subspecies of the collared lemming is complex but may be explained by a series of translocations between the original sex chromosomes and certain autosomes (figure 2). Thus *D.t.chionopaes* from Chukotka and *D.t.torquatus* from the Polar

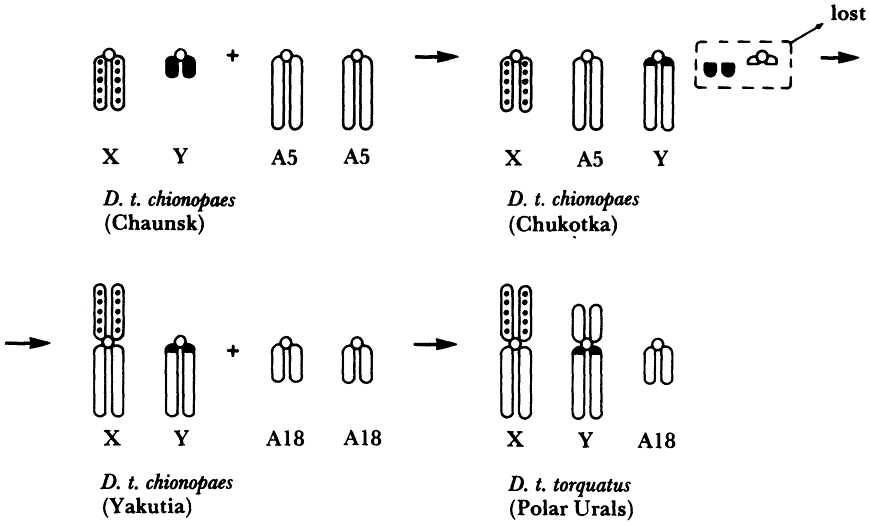

FIGURE 2. Sex chromosome evolution in *Dicrostonyx torquatus* from Siberia.

Urals have one chromosome less in XY males and X* Y females than in XX and X* X females, whereas all four sex-chromosome types of *D.t.chionopaes* from Chaunsk and from Yakutia have the same chromosome numbers. The elucidation of the sex-chromosome constitution in *Dicrostonyx* was further complicated by the presence of a varying number (0–15) of small B chromosomes (Gileva 1983).

It is remarkable that *Dicrostonyx* and *Myopus* have the same kind of X-linked mutations. This is in contrast to lemming species of the genera *Lemmus* and *Synaptomys*, which have ordinary XX/XY sex chromosomes. *Myopus* is phylogenetically much more closely related to *Lemmus* and *Synaptomys* than to *Dicrostonyx*. (*Synaptomys* is the ecological counterpart to *Myopus* in North America.) It therefore seems probable that mutations with similar effects have occurred on two separate occasions, and for unknown reasons have become established in populations all over the vast distribution range of *Myopus* and *Dicrostonyx*.

The X* chromosome leads to a skewed sex ratio in populations of these species. This is particularly evident in *Myopus* because their X* Y females almost always produce daughters only. Owing to a mechanism of double non-disjunction at mitotic anaphase in the foetal ovary of X* Y females, only X* eggs are formed. The X* Y females of *Dicrostonyx* produce both X*- and Y-carrying eggs, and consequently because of the early death of YY zygotes their litter size should be smaller than that of XX and X* X females. Theoretically the litter size of X* Y females should be reduced by one quarter compared with XX and X* X females, but thanks to a higher ovulation rate in X* Y females their reproductive output is not significantly lower than that of females with two X chromosomes (Gileva *et al.* 1982).

Why is the wood lemming such a good model for studies in sex determination?

The double non-disjunction mechanism in X* Y females of *Myopus* must be regarded as an evolutionarily advanced way to avoid reduced fertility in the X* Y females. However, the non-disjunction mechanism sometimes fails, and so Y-, X* Y- and O-carrying eggs are produced exceptionally, giving rise to XY males and X* XY, X* YY and XO individuals (Winking *et al.* 1981). Less common non-disjunction events at first or second meiotic division in males or females have also been documented by the occurrence of X* XX, XXY and X* O specimens.

The constitutions X* XY, X* YY and XO may also originate by meiotic non-disjunction, but the mitotic double non-disjunction in X* Y females must be the main cause of the high frequency of wood lemmings with abnormal sex chromosome constitutions. The frequency was 2.3% in laboratory stocks ($n = 1.600$) (Winking *et al.* 1981) and 3.0% in natural populations ($n = 270$) (Fredga *et al.* 1989). So far no XYY, XXX, X* X* Y or X* X* X individuals have been documented.

TABLE 3. KARYOTYPE, PHENOTYPE AND H-Y ANTIGEN STATUS OF WOOD LEMMINGS WITH DIFFERENT SEX CHROMOSOME CONSTITUTIONS (FOR REFERENCES SEE TEXT)

karyotype	phenotype	H-Y antigen status
32, XY	fertile male	+
32, XX	fertile female	−
32, X* X	fertile female	+
32, X* Y	fertile female	+
33, XXY	sterile male	n.t.
33, X* XY	sterile male	n.t.
33, X* XY	fertile female	n.t.
33, X* XY	true hermaphrodite	n.t.
33, X* YY	fertile female	n.t.
33, X* XX	(fertile) female	n.t.
31, XO	fertile female	+
31, X* O	fertile female	+

+, positive. −, negative. n.t., Not tested.

The various sex-chromosome types of normal and abnormal wood lemmings, their phenotypes and H-Y antigen status are listed in table 3. H-Y antigen typing has been done by serological and transplantation methods with concordant results (Wiberg *et al.* 1982; Wiberg & Günther 1985; Wiberg & Fredga 1985).

From a chromosomal point of view the following facts are of particular interest in connection with sex determination:

(i) The 33, X* XY individuals may be sterile males, fertile females or hermaphrodites (Winking *et al.* 1981), which demonstrates that this genotype is heterogeneously expressed. One true lateral hermaphrodite was found with a small undescended testis on the right side and an ovary on the left. Spermatogenic activity was completely lacking in the testis, whereas the ovary appeared normal. Winking *et al.* (1981) suggested that the variable phenotypic expression was a consequence of non-random inactivation of X and X*, with the two types either in unequal proportion or unequally distributed. Support for the non-random inactivation hypothesis was received from studies of the replication patterns of the X chromosomes in fibroblast cultures initiated from one X* XY male and one X* XY female (Schempp *et al.* 1985). The normal X was late-replicating (i.e. inactivated) in all cells of the female, whereas the mutated X* was late-replicating in all cells of the male. Thus it is likely that the actual gene (or genes) involved in sex determination does not escape inactivation.

(ii) The 33, X* YY individuals are normal fertile females. Thus two Y chromosomes cannot override the female-determining effect of X*.

(iii) The 31, X* O individuals are fertile females. This means that even in the absence of any sex-chromosomonally located sex-determining genes, a fully fertile female can develop.

In the light of recent findings by Page *et al.* (1987), the two last-mentioned types of wood lemming are of particular interest.

Page *et al.* (1987) identified a 140 kilobase DNA sequence on the human Y chromosome, which they considered to be the long-sought testis determining factor (*TDF*) gene. They also demonstrated the presence of a similar sequence on the human X chromosome. The sequences are not identical but could be functionally equivalent, possibly encoding similar finger proteins. They discuss four models for sex determination, of which Page is said to favour the dosage model (Roberts 1988). This model postulates that 'the X and Y loci are functionally interchangeable, both are testis determining and the X locus is subject to X-chromosome inactivation. According to this model sex is determined by the total number of expressed X and Y loci: a single dose is female determining while a double (or greater) dose is male determining' (Page *et al.* 1987). Our data in the wood lemming are not compatible with all aspects of this dosage model, provided that our prediction is correct, namely that it is the *Tdx* gene (= *TDFX* in man) that has been lost from the X* chromosome. Our findings may be summarized as follows.

1. The gene *Tdx* does not escape X-inactivation (X* XY, fertile females, sterile males or hermaphrodites, may be explained by non-random inactivation of X or X*).
2. One dose of *Tdx* gives rise to females (XO, fertile).
3. One dose of *Tdy* gives rise to females (X* Y, fertile).
4. No dose at all, neither *Tdx* nor *Tdy*, gives rise to females (X* O, fertile).
5. Two doses of *Tdy* and none of *Tdx* give rise to females (X*YY, fertile). I postulate that Y-chromosome inactivation does not occur in individuals with more than one Y chromosome.
6. Two doses give rise to males (XY, fertile; X* XY, sterile). The crucial point is that both alleles(?), *Tdx* and *Tdy*, must be present for normal male development.

It is possible to construct different models to explain the interaction between genes on the X and Y chromosome for male determination, for example *Tdy* and *Tdx* may encode similar but not identical proteins which together form a specific finger protein necessary for male development. Or finger proteins, encoded by *Tdy* and *Tdx*, may 'remove' different inhibitors along the route of male development, and not until both are 'removed' is a substance formed that switches off female development. However, as long as we do not know the molecular difference between X and X* of the wood lemming, it is too early to speculate in great detail. Research is in progress to find out whether or not *Tdx* is missing from X*.

Interaction between sex chromosomal and autosomal genes must of course also be considered. Polani (1981) concludes that in man more than two dozen major genes concerned with sex development, both 'determination' and 'differentiation', have been identified. Nevertheless, I think that there must be one simple and universal mechanism for normal sex determination in mammals. A Y chromosome, or at least a small part of it, is necessary for male development, but a normal X is equally important.

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Discussion

M. G. **Bulmer** (*Department of Biomathematics, University of Oxford, U.K.*). I should like to comment on the increased frequency of XY females in wood lemmings above the theoretical expectation of one third. Gileva (1987) has shown that there is a similar discrepancy in varying lemmings, and that it is due to preferential production or utilization of Y over X sperm. Might this also be happening in wood lemmings? Are there any relevant breeding data?

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Gileva, E. A. 1987 Meiotic drive in the sex chromosome system of the varying lemming, *Dicrostonyx torquatus* Pall. (Rodentia, Microtinae). *Heredity* **59**, 383–389.

F. **Fredga**. Yes, there are indications that offspring with a Y chromosome are born in excess also in the wood lemming. In *Myopus* 45% of the females are X*Y and not 33% as theoretically expected (Gropp & Winking 1982). The reason for this is unkown but I have data from my breeding colony showing that: (1) one XX line of females produced sons and daughters in a 2:1 ratio; in another XX line the ratio was the expected 1:1; (2) generally speaking, X*Y females give birth to more X*Y than X*X daughters. My breeding data are being analysed from different aspects, and experiments are in progress to elucidate the reason(s) for these deviations. Meiotic drive for the X* chromosome in X*X females may also account for a high frequency of X*Y females. Some X*X females produce a much higher frequency of daughters than the expected 3:1.

It should be mentioned that also in natural populations 45% of the females are X*Y ($n = 220$) (Fredga *et al.* 1989). This may, at least to some extent, be explained by differences in maturation rate, onset of reproduction and in pregnancy rate of the different female types. In all these attributes the X*Y was superior to X*X, which was superior to XX in a natural population studied by us (Bondrup-Nielsen *et al.* 1989).

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