# The evolution of the peculiarities of mammalian sex chromosomes: an epigenetic view

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## Summary

In most discussions of the evolution of sex chromo-somes, it is presumed that the morphological differ-ences between the X and Y were initiated by genetic changes. An alternative possibility is that, in the early stages, a key role was played by epigenetic modifications of chromatin structure that did not depend directly on genetic changes. Such modifications could have resulted from spontaneous epimutations at a sex-determining locus or, in mammals, from selection in females for the epigenetic silencing of imprinted regions of the pater-nally derived sex chromosome. Other features of mam-malian sex chromosomes that are easier to explain if the epigenetic dimension of chromosome evolution is con-sidered include the relatively large number of X-linked genes associated with human brain development, and the overrepresentation of spermatogenesis genes on the X. Both may be evolutionary consequences of dosage com-pensation through X-inactivation. *BioEssays* 26:1327–1332, 2004. © 2004 Wiley Periodicals, Inc.

## Introduction

While the role of epigenetic inheritance in development is becoming a major subject of biological research, the study of its implications for evolution is lagging far behind. The direct role of heritable epigenetic variants in evolution is largely ignored, and their indirect effects are treated as peripheral. Although the Lamarckian aspects of epigenetic inheritance may be responsible for the reluctance to consider its direct effects on evolutionary change, the indirect effects do not threaten orthodoxy, so their neglect is probably simply a reflection of the inertia associated with the dominant gene-centred paradigm. The result, however, is that even though there are many evolutionary problems for which epigenetic inheritance is likely to be relevant, discussions of its role and effects are largely confined to two well-known epigenetic phenomena—genomic imprinting and X-chromosome inacti-vation. Even in cases such as the evolution of the mammalian sex chromosomes, which undergo such striking epigenetic

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changes during development, evolutionary explanations of their peculiar organisation and gene content commonly ignore the epigenetic aspects (e.g. see Vallender and Lahn[1]).

In this review, I want to show how considering epigenetic inheritance can lead to additional evolutionary interpretations of some of the well-known and widely discussed properties of mammalian sex chromosomes. I shall consider three topics: the degeneration of the Y chromosome, the relatively large number of genes affecting intelligence on the human X and the observation that the X is rich in genes affecting spermatogenesis. My purpose is not to argue that these epigenetics-biased interpretations are better than the conven-tional gene-biased ones, but to show how an epigenetic per-spective can suggest alternative or complementary answers to some evolutionary questions.

## Background

In most species with chromosomal sex determination and heterogametic males, the Y chromosome is small and gene-poor. Its degeneration from a normal chromosome is thought to have begun with reduced recombination between a proto-Y and proto-X that differed genetically at a sex-determining (S-D) locus.[1,2] This reduction in recombination may have been the outcome of selection against crossing-over between alleles linked to the S-D locus that had different effects in males and females,[2] or it could have resulted from an inversion or conformational change in chromatin that impaired meiotic pairing.[3,4] Once recombination was reduced, Muller's ratchet, genetic hitchhiking and comparable processes led to the accumulation of deleterious recessive alleles on the Y, and this functional impairment eventually resulted in the Y chromo-some's physical degeneration.[2]

The deterioration of the Y was associated in some taxa with the development of mechanisms that equalised the dosage of X-linked genes in male (XY) and female (XX) individuals. In mammals, this dosage compensation was brought about by the inactivation of one of the two X chromosomes in female cells.[5]

Studies comparing the chromosomes of different mam-malian groups provide a glimpse of the possible stages in the evolutionary degradation of the Y and the development of dosage compensation through X inactivation.[3] In the prototherians (monotremes), the X and the Y are similar in

length and G-banding, the only difference being the length of the short arm. The short arm of one of the X chromosomes in female platypus and echidna lymphocytes is also late replicating, suggesting that, in monotremes, it is also inactive. In marsupials (metatherians), the X and the Y are distinctly different, with the Y chromosome showing extensive degeneration. The paternal X of female marsupials is preferentially inactivated in all tissues, although this inactivation is not as complete and robust as that seen in eutherian mammals, where X-chromosome inactivation is random. Parts of eutherian X chromosomes are homologous to the X of monotremes and marsupials, but they also carry genes that are autosomal in these groups, and were presumably translocated to the eutherian X after the three major mammalian groups diverged.

## What leads to Y chromosome degeneration in mammals?

I shall suggest two scenarios for Y degeneration in mammals, both of which start with the assumption that the initiating event was epigenetic and genetic changes followed. The epigenetic event could have been a heritable change in the pattern of histone modifications, or in DNA-associated non-histone proteins, or in DNA methylation. Both of my scenarios also incorporate the observation that the conformational changes that occur in all chromosomes during meiosis and gamete formation are markedly different in males and females.[6] This is believed to be the basis of the parent-of-origin-dependent differences in gene expression known as genomic imprinting, which is part of the second scenario. Genomic imprinting is well known in mammals,[7] and experimental manipulations with *Drosophila* have shown that, when a Y chromosome is forced to go through female gametogenesis, the expression of the genes that it carries is altered.[8]

### (i) Initiation by epigenetic inactivation of the S-D locus

Jablonka and Lamb[4] and Gorelick[9] have suggested that the first step in the differentiation of the sex chromosomes was epigenetic silencing of an S-D region in one of a pair of morphological identical chromosomes. This silencing could have been the result of an accidental epimutation, or possibly the outcome of epigenetic marks (such as methylation changes) that accumulated because, by chance, the chromosome had been transmitted repeatedly through males. Initially silencing did not involve DNA sequence changes, but it was meiotically heritable (i.e., it was a stable epimutation), and hence male sex-determination became constitutive. Such an evolutionary origin of the Y is mechanistically plausible because the transmission of an epigenetically silenced state of chromatin through meiosis is well documented for a variety of well-studied organisms, including plants, yeast, insects and mammals.[10–12] Furthermore, a changed epigenetic mark on

a proto-Y chromosome is particularly likely to persist, because the chromosome that leads to male development is transmitted only through males, and hence experiences only the conformational changes related to spermatogenesis. Epigenetic marks on the proto-Y are therefore not constrained by the very different structural and functional requirements of oogenesis.

The type of locus that may have initiated differentiation of the Y is a major *cis*-acting repressor (a Xist-like locus) whose inactivation allowed the male-determining gene to become active. Following the epigenetic inactivation of this repressor locus, the pattern of gene expression on the proto-Y—Xist-like gene inactive, male-determining gene active—would result in constitutive expression of male characteristics in animals inheriting this chromosome. However, if this pattern persisted into meiosis, there would have been a lack of conformational homology with the proto-X, which retained the original pattern of gene expression—Xist-like gene active, male-determining gene inactive. Such conformational differences between homologous regions of chromosomes can lead to meiotic pairing failure and a consequent reduction in fertility, but the pairing problem is avoided if, as commonly happens, the incompatible active regions are inactivated during meiosis.[4,6]

Once both homologous regions have an inactive, heterochromatic conformation during meiosis, recombination between them is reduced. Therefore, in the scenario just described, reduced recombination in the S-D region of the sex chromosomes of the male was a by-product of meiotic inactivation, and does not require an independent explanation. Reduced recombination resulted in the accumulation of detrimental genetic and epigenetic variations, and hence led to functional decay in this region of the Y.[2] Only genes like the male-determining locus, which are expressed and under selection in the male, escaped the deterioration of the Y. The corresponding region of the X did not suffer the same fate, because the paternally derived X is reactivated in females, and recombination occurs between the two X chromosomes.

Once in place, the constitutively heterochromatic, non-recombining region of the Y allowed inversions within and slightly beyond it to become established, because heterochromatin-associated suppression of recombination prevented the crossing-over within inversions that usually leads to aneuploid gametes and hence to selective elimination of chromosomes with inversions. As genes in the permanently inactivated region of the Y gradually deteriorated, there was further compensatory developmentally regulated X-inactivation during male meiosis. This, in turn, led to even less recombination, to the degeneration and loss of more genes on the Y, and so on.

A further consequence of meiotic inactivation of the X in the male was that, in the offspring inheriting it (which were necessarily female), there were conformational differences between the paternally derived X ($X^p$) and maternally derived

X ($X^m$) chromosomes. In other words, these chromosomes carried strong epigenetic marks reflecting the sex of their parent of origin—they were imprinted. The selection of maternal factors that stabilised the meiotically transmitted inactive state of $X^p$ and led to its mitotic inheritance became the basis of the dosage compensation in mammals. As the decay of the Y progressed, it was accompanied by a progressive dosage compensation of the X-linked genes.[3,4,13–15]

The scenario for Y degeneration that I have just outlined is not specific to mammals. It can be applied to any taxon with heteromorphic sex chromosomes and a Y that is inactive and heterochromatinized in male meiosis.[4] An indication of whether epigenetic events had a role in the early stages of the morphological differentiation of the X and Y may come from studies in which the chromatin structure and DNA sequences of species with sex chromosomes of equal size are compared with those of related species with Y degeneration. The relatively recent origin of the sex chromosomes of dioecious plants and the availability of closely related species that lack them make plants especially suitable for such studies,[16] and there is already evidence that experimentally induced epigenetic changes can influence their sexual phenotypes.[17] Some insects, fish, amphibians and reptiles also have sex chromosomes that seem to be at a relatively early stage of differentiation,[4] and molecular studies of these chromosomes should be informative. Perhaps the most-telling information will come from studies of species in which in some populations sex determination is 'environmental' and in others it is 'genetic'. According to the present hypothesis, in some of the latter populations, the heritable difference between chromosomes with S-D regions may well be epigenetic, rather than genetic. The suggestion made earlier that a changed epigenetic mark might arise when a chromosome is transmitted for many generations through the same sex can be tested experimentally.

It may be difficult to obtain evidence that would enable one to discriminate between the present hypothesis for Y degeneration, which is based on an initial epigenetic change, and one based solely on genetic changes, but this is not a good reason for automatically assuming that genetic changes have primacy. In fact, the hypothesis of an epigenetic beginning might be preferred, because it has the advantage of parsimony: reduced recombination is a necessary by-product of the epigenetically inactivated heterochromatic region and already-evolved processes that ensure appropriate meiotic pairing and segregation, so there is no need to invoke additional genetic or epigenetic changes to suppress recombination.

### (ii) Genomic imprinting as an initiating process in the degeneration of the Y

There is an additional mechanism—maternal inactivation of imprinted regions—that could have been involved in the evolutionary degeneration of the mammalian Y chromosome. As with the previous scenario, this one depends on the single-sex transmission of genes on the Y but, in this case, the initiating changes in epigenetic marks might have had nothing to do with the S-D locus. Unlike the first scenario, this one is specific to mammals, and cannot be applied to other animal taxa.

The proposed mechanisms of Y degeneration is based on Moore and Haig's hypothesis,[7] which suggests that, where there is multiple paternity (as there is in most mammal species), there is a conflict of interest between maternally and paternally derived alleles within the embryo. Paternal alleles will be selected to extort as much nutrient from maternal tissues as possible, because the relationship between a father and some of his offspring's sibs (who were fathered by a rival male) may be zero, and he has no interest in their welfare; however, it is in the mother's interest to share her resources equally among the offspring, to all of whom she is equally related. Such conflicting interests lead to an arms race between paternal imprints that promote the acquisition of extra nutrients by the embryo, and maternal imprints and/or zygotic factors that prevent or suppress the excessive growth demands effected through paternally imprinted genes.

The scenario starts from a situation in which sex was already genetically determined, but as yet there was no or an insignificant size difference between the sex chromosomes. It is assumed that these proto-X and Y chromosomes had, in addition to the S-D locus, a growth-affecting cluster of genes in a region that was imprinted in the father to make his embryos 'greedy'. As maternal post-zygotic investment in offspring grew during mammalian evolution, so did selection for effective maternal 'retaliation'. Like Moore et al,[18] I assume this was achieved by the inactivation of the 'greedy-gene' region of the paternally derived sex chromosomes ($X^p$ in females and Y in males) through factors in the zygote. In most somatic cells, this zygotically imposed inactive state (associated with late replication and heterochromatinization) persisted throughout development for both the $X^p$ (in female offspring) and Y (in male offspring). In females, the inactive $X^p$ region had to be reactivated and euchromatinized during oogenesis to allow the transcription of essential X-linked genes and enable normal meiotic pairing and recombination between the two homologues.[6]

From this point onward, this scenario follows the same sequence of events as that described in the previous one. First, since the Y is transmitted exclusively through males and is never required to undergo conformational reprogramming in the opposite sex, females could impose strong inactivation on the greedy-gene region of the Y. Second, when this inactivation persisted into meiosis, the different conformations of the region—active in the X and inactive in the Y—led to the heterochromatinization early in meiosis of the greedy-gene region of the X, because in this way the problems of pairing

failure were avoided.[4,6] Third and finally, this led to reduced recombination, the accumulation of detrimental alleles and epialleles, and the functional decay of the differentially expressed region of the Y chromosome. Such imprinting-driven Y deterioration may have happened more than once during mammalian sex chromosome evolution if, as the evidence suggests,[19] there were several translocations from the autosomes to the sex chromosomes, and these included imprinted domains. This scenario is consistent with the far greater homology of the X and Y in monotremes, where there is no opportunity for prenatal conflicts for resources (although some might be expected postnatally), and no evidence of parental imprinting has been found.[20] If correct, this scenario suggests that Y degeneration followed (rather than preceded) the evolution of imprinting.

The two scenarios that I have outlined are not mutually exclusive. If an imprinted region was closely linked to the S-D locus, then, through position-effects that spread and stabilise the inactive state of a neighbouring region, such linkage could have reinforced and accelerated the rate of Y degradation. Both scenarios are consistent with what is known about the conformational changes that take place in the sex chromosomes of mammals,[4,6] and also with the observation that, right from the zygote stage, the $X^p$ of the mouse is only partially active.[21] In other words, the mouse $X^p$ seems to retain marks of its spermy past. In the extraembryonic tissues, the $X^p$'s partial inactivity is stabilised and it becomes fully inactive, whereas in the embryo proper there is brief re-activation of the $X^p$ followed by random inactivation of one of the Xs. Preferential inactivation of the $X^p$ in the extraembryonic tissues of mice must therefore be based on the retention, recognition and stabilisation of marks conferring inactivity that are carried-over from the sperm. According to the first scenario, this is the outcome of selection for dosage compensation as the Y deteriorated; according to the second (imprinting) scenario, it is the result of selection for maternal factors that favoured retention of the inactive state of the $X^p$ to avoid excessive maternal exploitation, and only later became involved in compensating for the dosage differences following the elimination of Y genes.

If the epigenetic-based proposals are correct, one prediction is that the imprinting of the $X^p$ would be a gradual process that went hand in hand with the degeneration of the Y, and that inversions on the Y would usually follow, rather than precede, heterochromatinization. Where there is evidence, as there is for mammals, that parts of ancestral autosomes have been translocated to the sex chromosomes,[19] any imprinted genes in these translocated blocks should no longer have functional homologues on the Y, because they would have been the first to degenerate. Comparisons of imprinted regions of marsupials and placental mammals could test this hypothesis. Since the arguments about the persistence of inactivation in imprinted sex-linked genes may also apply to

flowering plants, the loss of imprinted regions on the degenerate sex chromosome is also expected to be an early stage in the chromosomal differentiation process in plant groups with a heteromorphic Y.

## Selection of X-linked genes in mammals: why are there more 'brain-genes' on the X?

One of the interesting things that the sequencing of the human genome has revealed is the relatively large number of genes associated with brain development that are on the X chromosome.[22] Vallender and Lahn suggest that the most plausible explanation of this is that it is a consequence of sexual selection.[1] They argue that at some time in our evolutionary past, males with the greatest cognitive capacity (or possibly just larger heads) were able to win or seduce most females. Recessive genes that could contribute to their big brains and were located on the X chromosome were rapidly selected and fixed, because their hemizygosity in males meant that, unlike autosomal recessives, they were always visible to selection. Any beneficial effects that they eventually had for females are assumed to be incidental: for as long as females were heterozygous, these X-linked alleles were invisible to selection.

The problem with the latter conclusion is that it overlooks the effects of the mammalian method of dosage compensation through X-inactivation. The argument assumes that new X-linked recessive alleles are, like autosomal recessives, visible to selection in females only when the females are homozygous. This error has been perpetuated in the literature at least since the publication of the influential paper by Charlesworth et al.[23] The reasoning in that paper is based on the assumption that a recessive mutation on the X in dosage-compensated females has the same effects as such a mutation would have had, had it been on an autosome. This leads the authors to conclude that: 'When selection is restricted to the homogametic sex, dosage compensation is largely irrelevant, and favourable mutations accumulate at approximately equal rates on the X chromosome and autosomes' (ref. 23, p. 126). The same reasoning is reflected in Vallender and Lahn's claim that: 'Sexually antagonistic genes beneficial to the homogametic sex are only slightly more likely, if at all, to become fixed on the homogametic sex chromosome than on autosomes' (ref. 1, p.165). Both sets of authors are wrong when their reasoning is applied to mammals, because of the method of dosage compensation. When dosage compensation is through paternal X inactivation, as it is in marsupials, any recessive mutation in females (the homogametic sex) is fully exposed to selection in those females that inherit it from their mother. It behaves as a dominant in such females. When dosage compensation is through random X-inactivation, as in eutherian mammals, females that are heterozygous for X-linked genes may have an intermediate phenotype, because in ~50% of their cells one allele is expressed, and in ~50% the

other. So if, for example, the expression of a new X-linked allele is beneficial because it leads to more dendritic branching, nervous tissue could be a mosaic of cells, half of which express the new allele and have more dendrites, and half of which express the old allele and have fewer. The actual phenotype seen in heterozygotes for a new X-linked allele will depend on whether its effect is cell-autonomous or tissue-dependent, on the nature of the dependence (if any), on selection between cells during development, and so on. Nevertheless, however complicated the interrelations in the mosaic of the two cell types that are generated by random X-inactivation, the assumption that in females a newly arisen X-linked, potentially beneficial, 'recessive' allele will not be exposed to selection is unwarranted. The rate of evolution of chromosomes with beneficial semi-dominant alleles is in theory high (e.g. see ref. 24, pp. 44–45). The mistake in treating the selection of X-linked alleles in females as similar to the selection of auto-somal alleles is probably due to extrapolation from *Drosophila*, where dosage compensation is achieved by doubling the transcription rate of X-linked genes in males, and X-linked recessives in females are indeed shielded from selection. It is, however, clearly wrong for mammals.

Since 'recessive' X-linked alleles in human females are subject to dosage compensation and are expected, on average, to have semi-dominant effects, an explanation of the high proportion of brain-related genes on the X in humans might start from rather different assumptions from those suggested by Vallender and Lahn. One could assume, for the sake of argument, that being 'brainy' is more important for mammalian females than for males, because the prolonged maternal care females give to their young is cognitively very demanding. Consequently, there will be intense selection in females for alleles that improve cognition. In males the same alleles may be neutral or incidentally beneficial; if beneficial, they will be selected in males too. Of course, as Vallender and Lahn point out, there is absolutely no need to assume that genes that contribute to cognitive abilities confer advantages preferentially on a single sex. In general, it is expected that beneficial alleles affecting adaptive traits that would have had recessive effects had they been on autosomes, will tend to accumulate on the mammalian X because, through expression in mosaic females and/or in hemizygous males, they will have more chance of reaching fixation than they would have had, had they been on autosomes. Increased intelligence, reflected among other things in an increase in relative brain size and in the complexity of social groups, seems to be a trend in social mammals in general and the hominid line in particular.[25] Hence, it is reasonable to assume that persistent selection for increased intelligence was particularly important. Since, for several reasons, most new mutations are recessive,[26] the accumulation on the X chromosome of beneficial 'recessive' genes contributing to this adaptive trend in hominids is expected. In fact, according to the present hypothesis, genes for any trait in mammals (e.g. size) that shows a persistent adaptive trend are likely to have a disproportionately large representation on the X.

## Why are there more 'spermatogenesis-genes' on the X?

Genes affecting spermatogenesis are over-represented on the mammalian X chromosome.[27] The most-likely reason for this is that genes affecting male-specific functions escaped Y degeneration and evolved rapidly because they were exposed to selection in hemizygous males[1,2] However, in mammals there could be an additional and complementary contributing factor. Genes that are spermatogenesis-specific are sex-limited in their expression: either they are not expressed at all in females, or they are expressed only in different tissues or at a different stage of development. Whether they are on the X chromosome or on autosomes, spermatogenesis genes have to be silent in females when active in males. However, with X-linked genes, because of X inactivation, only one of each pair of alleles in a cell (that on the active X) has to be silenced, rather than the two alleles that have to be silenced with autosomal genes. Holliday has suggested that functional hemizygosity, whether due to imprinting or stochastic allelic exclusion, may be generally beneficial whenever the accurate control of gene expression is required.[28] Since it is important to suppress spermatogenesis genes effectively in females, the accumulation of these genes on the X chromosome may reflect the selective advantage of mono-allelic control of male-limited genes in females, as well as the rapid selection of beneficial male-limited alleles due to their hemizygosity in males. This hypothesis would be supported if sex-limited genes on autosomes were found to be expressed mono-allelically more often than genes that are not sex-limited.

## Conclusions

The cases examined here illustrate how incorporating an epigenetic dimension can expand and sometimes change the range of interpretations offered for evolutionary phenomena such as the origins of heteromorphic sex chromosomes and the spectrum of genes found on them. Whether or not the additional explanations that I have suggested are valid should become clearer as more information about genetic and epigenetic aspects of sex chromosomes is obtained. Until that time, I believe it is unwise to assume genetic changes alone are the basis of all evolutionary changes in sex chromosomes.

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