How mammalian sex chromosomes acquired their peculiar gene content

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Summary

It has become increasingly evident that gene content of the sex chromosomes is markedly different from that of the autosomes. Both sex chromosomes appear enriched for genes related to sexual differentiation and reproduction; but curiously, the human X chromosome also seems to bear a preponderance of genes linked to brain and muscle functions. In this review, we will synthesize several evolutionary theories that may account for this nonrandom assortment of genes on the sex chromosomes, including 1) asexual degeneration, 2) sexual antagonism, 3) constant selection, and 4) hemizygous exposure. Additionally, we will speculate on how the evolution of sex-chromosome gene content might have impacted on the phenotypic evolution of mammals and particularly humans. Our discussion will focus on the mammalian sex chromosomes, but will cross reference other species where appropriate. ***BioEssays*** **26:159–169, 2004. © 2004 Wiley Periodicals, Inc.**

Introduction

Across species, autosomes seem rather comparable to one another. Some are large and some are small; some are gene rich and some gene poor. All, however, seem to share the same basic characteristics. In any given species, the unique cytogenetic pattern between homologous autosomes is the same and, while genes of similar function may have a tendency to cluster,[1] the genes of an autosome are more or less a random subset of the entire species' genome.

Not so for the sex chromosomes. In many, though not all, species, the sex chromosomes look very unlike one another. The human X chromosome is roughly three times the size of the human Y chromosome and its constituent chromatin is so different as to appear unique even cytogenetically. On the genic level, the X chromosome has several magnitudes more genes than the Y chromosome. Further, the kinds of genes that one finds on the sex chromosomes are not only different from each other, they are also quite different from the autosomes. Indeed, it has been repeatedly shown that the genes present on the sex chromosomes are not random subsets of the genome.

Sex chromosomes are neither universal nor necessary. In many species, sex is determined by environmental cues rather than by genetic ones. In many extant reptiles, for instance, sex is determined by the temperature during embryonic development.[2] From a phylogenetic perspective, it seems clear that the last common ancestor of mammals, birds, and reptiles had an environmentally based sex-determination system. At some point during the emergence of both mammals and birds, a transition was made to a genetically based system, though this occurred on separate occasions.

Sex-chromosome systems are extraordinarily labile.[3] They have evolved independently many times in disparate lineages, including plants, insects, fish, birds and mammals. The mechanisms by which they arise are equally diverse. Traditionally, most sex-chromosome systems belong to either the XX:XY system (in which males are the heterogametic sex), or the ZZ:ZW system (where females are heterogametic). There can, however, be further elaboration on these basic schemes, including for example, X_1X_2Y, XY_1Y_2, and ZW_1W_2 systems found in neotropical freshwater fish.[4] The sex-determination system can even change within species. XY females, in which sex is determined primarily by an X chromosome haplotype, are observed in several mammalian species.[5] Species have even been observed in which both XX:XY and ZZ:ZW systems are present.[6]

The reason, in part, for this extraordinary lability in sex determination is resultant from the nature of sex determination itself. The process of sex determination is regulated by complex pathways of many genes scattered among many chromosomes. The origins of genetic sex determination can occur when any gene within the web of sex-determination pathways generates an allele which gives rise specifically to

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Abbreviations: X, X chromosome; Y, Y chromosome; XO, monosomy of the X chromosome; NRY, non-recombining portion of the Y chromosome.

either males or females. The nature of these sex-determination pathways are very complex and beyond the scope of this review though it has been treated in depth elsewhere.[3,7]

As noted, mammalian sex chromosomes are heteromorphic (that is, they differ significantly in physical appearance). Heteromorphism is not necessary among sex chromosomes however. Indeed it appears that heteromorphic sex chromosomes evolve from homomorphic sex chromosomes (i.e. sex chromosomes that appear identical, but have a single segregating sex determining gene). This process has been observed from monotremes to marsupials to placental mammals with the former being the most homomorphic and the latter being the most heteromorphic.[8] The mechanisms by which sex-chromosome hetermorphy occurs will be addressed subsequently.

The mammalian X and Y chromosomes appear to have diverged from a pair of autosomes approximately 300 million years ago, shortly after mammals diverged from their reptilian ancestors.[9] This ancestral autosome pair is thought to have been generally unremarkable in gene content. Their transition to the status of sex chromosomes is believed to have been triggered by mutational events that converted an otherwise unimpressive autosomal member of the environmental sex determining pathways, *SOX3*, to the male-determining gene, *SRY*.[10,11] In this regard, *SOX3* and *SRY* can be viewed as two alleles of the same locus during the very early stage of sex-chromosome evolution, with the *SRY*-bearing autosome becoming the nascent Y chromosome, and its *SOX3*-bearing partner becoming the nascent X. The Z and W sex chromosomes of birds, however, share homology not with the human X and Y, but rather with human chromosome 9.[12] So obviously, the *SOX3/SRY* duo can't possibly be the primary determinant in differentiating the avian sex chromosomes and thus the sexes. It has been very tentatively speculated that another gene in an ancestral sex determining pathway, *DMRT1*, may have diverged into Z- and W-specific forms in birds, creating a genetic system of sex determination.[13,14]

Even though the emergence of sex chromosomes has taken place independently in many different lineages, their fate seems to follow a similar evolutionary trajectory. The mammalian Y chromosome and the avian W chromosome, both of which occur only in hemizygous state in the heterogametic sex (and are hence known as the heterogametic sex chromosomes), are significantly smaller than typical autosomes, largely heterochromatic, and exceptionally gene poor. Conversely, the X and Z chromosomes, which are homozygous in the homogametic sex (and are therefore known as the homogametic sex chromosomes), are generally comparable in size and gene density to autosomes, a condition presumably on par with their ancestral state.

It is increasingly noted that the sex chromosomes, unlike the autosomes, harbor an excess of genes belonging to limited functional categories.[15] At least four major evolutionary processes may underlie this phenomenon. Asexual degeneration, long recognized and best understood, predicts a generalized loss of genes from the heterogametic Y (or W) chromosome due to the absence of meiotic recombination.[16] Sexual antagonism, the condition in which a gene enhances fitness in one sex but lessening it in another, predicts masculinization of the Y and feminization of the X. Constant selection also argues for masculinization of the Y due to the Y's constant presence in the male but never female context, and feminization of the X due to its spending more time in females than males. Finally, hemizygous exposure attempts to explain the curious observation of some masculinization of the X by arguing that recessive mutations benefiting males may rise to fixation more readily if they occur on the X (which is hemizygous in males) than if they occur on autosomes. Some of these evolutionary processes can have opposite effects on gene content of the sex chromosomes. For example, sexual antagonism can lead to feminization of the X, while hemizygous exposure may result in its masculinization. In the final analysis, therefore, the peculiar gene content of the sex chromosomes may well be the net outcome of multiple—and sometimes opposing—evolutionary forces operating within these unusual territories of the genome. This review will attempt to synthesize contemporary thoughts on how each of these evolutionary forces may have operated. But before that, a brief account of sex-chromosome biology is in order.

The Y (or W) chromosome

The Y chromosome typically contains two distinct domains: the terminal pseudoautosomal region (or PAR, which sits at one or both ends of the chromosome and still recombines with corresponding pseudoautosomal regions of the X), and the centrally located non-recombining region (or NRY, which does not recombine with the X and therefore follows strict patrilineal inheritance). In humans, the PAR comprises only about 5% of the Y chromosome, with the remainder of the chromosome falling within the NRY.

Evolution of the heterogametic Y chromosome is characterized by widespread degeneration, along with a concurrent accretion of genes with male-specific functions. Degeneration results from the lack of meiotic recombination, and therefore only affects the NRY portion of the Y chromosome. In humans, the consequence of degeneration is a Y chromosome that is both physically small (~30 Mb of euchromatic DNA, or around 1% of the genome), and gene poor (only about 50 distinct genes or gene families). The pseudoautosomal arms, though representing only a small fraction of the human Y chromosome, contain approximately one third of all the distinct genes/families found on this chromosome. The pseudoautosomal genes are in many ways typical of those found elsewhere in the genome, insofar as they appear to have a diverse functional portfolio. The remaining genes, located on the NRY, show a very limited range of

expression patterns, and frequently seem to be involved in male-specific functions such as sex determination or spermatogenesis.[17,18]

Genes of the human NRY can be further divided into three categories[19] (see Table 1). NRY class 1 genes generally have housekeeping functions, broad tissue expression, and an active X homolog. NRY class 2 genes are involved primarily in spermatogenesis, expressed exclusively in the testes, have multiple copies on the Y chromosome, and lack an active X homolog. NRY class 3 genes fall somewhere in between the first two classes. These genes show a more diverse array of function and expression (though they do exhibit a greater proclivity towards expression in the testes), and also have an active X homolog. Thus, NRY genes exhibit an overall trend of masculinization by virtue of their propensity for testis-specific expression and function.[19] The preponderance of X-Y homologous genes, regardless of their expression pattern, also attests to the common origin of the two sex chromosomes. By analyzing these X-Y genes, it is recognized that the evolutionary history of the mammalian sex chromosomes was demarcated by several discrete, en bloc expansions of the NRY.[9] Such large-scale expansions of the non-recombining region may also apply to the evolutionary history of the W chromosome in the ZZ:ZW system.

Recently, it has been suggested that the Y chromosome harbors within it genic "alleles" in the form of paralogous copies.[20] Large palindromic sequences are observed on the chromosome which may, via gene conversion, effectively act as alleles for the genes specifically residing on the Y. This may explain in part the large copy number seen in NRY class 2 and some class 3 genes (Table 1). Although the origins and indeed the very existence of these motifs are only recently becoming understood, this process may prove to be one of the most intriguing to affect the Y chromosome.

While sex in *Drosophila* is determined by the X-to-autosome ratio and is independent of the Y, there remains a small Y chromosome (although given its dubious origins perhaps it is better characterized as a small chromosome functionally equivalent to the Y) comprising less than 3% of the total genome.[21] The fly Y carries few genes and is therefore also considered a victim of functional decay (though again due to the dubious origins of the *Drosophila* Y the extent of this functional decay may be greatly limited when compared to that seen in mammals).[22] Nine single-copy genes have been identified on the fly Y, with a reasonable guess that at least this many will be identified in the future.[23] Strikingly, all these genes show evidence of male-related functions. They do not appear to have X homologs, though they do seem to have autosomal homologs. In this regard, these *Drosophila* Y-linked genes are very similar to the NRY class 2 genes of the human Y.

The X (or Z) chromosome

The X chromosome, unlike the Y chromosome, typically appears outwardly similar to autosomes. The human X, for example, is ~160 Mb in size, essentially all euchromatic, and contains close to 2000 genes. This places the X among the larger chromosomes in the human genome, with a gene density slightly lower but roughly on par with autosomes. While the relative paucity of genes on the Y chromosome has made it especially amenable for discerning patterns of gene composition, the similarity in gene density between the X chromosome

Table 1. Genes in the non-recombining region of the human Y chromosome

Gene category	Gene	Function	Expression	Multiple closely related Y copies?	X homolog?
NRY class 1	*ZFY, UTY, DBY, TMSB4Y, SMCY, RPS4Y1, RPS4Y2, CYorf15A, CYorf15B, USP9Y, EIF1AY, PRKY*	Housekeeping	Ubiquitous	No	Yes
NRY class 2	*BPY2, CDY, DAZ, HSFY, PRY, TSPY, XKRY*	Spermatogenesis	Testis	Yes	No
NRY class 3	*RBMY*	Spermatogenesis	Testis	Yes	Yes
	VCY	Unknown	Testis	Yes	Yes
	SRY	Male determination	Testis	No	Yes
	TGIF2LY	Unknown	Testis	No	Yes
	HSFY	Transcription factor	Testis	No	Yes
	NLGN4Y	Cell adhesion	Testis, Brain, Prostate	No	Yes
	TBL1Y	Protein-protein interactions	Brain, Prostate	No	Yes
	PCDH11Y	Brain development; cell-cell adhesion and signalling	Brain	No	Yes
	AMELY	Tooth development	Tooth bud	No	Yes

and autosomes has initially masked any such patterns. Recent work, however, has indicated that there are indeed functional themes in the gene content of the X chromosome, with certain classes of genes systematically over-represented and other classes under-represented.[24]

One of the first categories of genes to be extensively studied was those involved in sex and reproduction. Using publicly available data, it was noted that a greater proportion of sex- and reproduction-related traits mapped to the human X chromosome than to autosomes. Of 141 disease-related loci on the X chromosome, 46 are related to sex or reproduction as compared to 26 of 264 for the autosomes.[25] However, this observation should be viewed with some caution, as it may be partly due to the preferential ability to map certain types of genetic diseases to the X chromosome. Another less-biased study identified 25 genes expressed uniquely in the early stages of male germ cell development (*i.e.*, the spermatogonia).[26] When mapped, three of these genes localized to the mouse Y chromosome and 10 to the X, much greater than the 0 and 2 expected by random chance. Thus, it appears that the mammalian X chromosome, like the Y, shows an over-representation of genes involved in sex and reproduction (including, curiously, male reproduction; see later discussion). It is worth noting, however, that unlike the Y, the X also harbors many genes unrelated to sex and reproduction, which should be functionally important to both sexes.

In contrast to the Y chromosome, the human X shows a preponderance of other types of genes as well. It has long been noted that in humans at least, the X chromosome appears to have a large effect on brain development. Using brain transcriptome analysis, certain regions of the X have been found to be enriched for brain expression.[27] Over 10% of human X-linked genes appear to be associated with mental retardation, more than three times the autosomal average and more than two times the highest autosome.[28] In addition, presumably due to X chromosome hemizygosity, males are 25 to 30% more likely to show mental retardation than females,[29] and have a greater variance in standard tests of intelligence.[30] Intriguingly, several connections between brain function and sexual function have been observed. Many genes appear to show co-expression in testis and brain (this is the popularly quipped brain–testis connection).[31] Additionally, mental retardation tends to be associated with defects in testis function, with about 14% of all mental retardation diseases also showing hypogonadism, cryptorchidism, or macroorchidism.[28]

The human X chromosome also shows an excess of skeletal-muscle-related genes. A study of the human skeletal muscle transcriptome identified three chromosomes with statistically significant overrepresentation: chromosomes 17, 19 and X.[32] A total of 1078 skeletal muscle transcripts were identified of which 41 were located on the X chromosome, a value significantly greater than the 29.5 expected by chance. Thus, skeletal muscle genes, along with sex and reproduction genes and genes involved in the brain, appear to be enriched on the human X chromosome.

The *Drosophila* X chromosome gene content has also been studied extensively, though with different results relative to the human X. The *Drosophila* X comprises nearly a fifth of the total fly genome and again shows a gene density similar to that of autosomes. Using a cDNA array to differentiate between genes showing either male-biased or female-biased expression, it has been demonstrated that the fly X chromosome shows significantly lower proportion of genes with male-biased expression.[33] Interestingly, this same study finds an over-representation of male-biased genes on the 2L chromosome arm and a random distribution of female-biased genes. Other work has shown similar results with testes-specific genes clustering non-randomly in the *Drosophila* genome.[34] These data seem to be in apparent opposition to that seen in humans where there appears to an enrichment of certain male-related genes on the X and in which the autosomes do not show an excess of these genes (this issue is discussed later).

A similar study has been undertaken in *Caenorhabditis elegans*, a species with an XX:XO system of sex determination, but in which hermaphroditic XX females are the norm with only a small number of XO males maintained in natural populations.[35] Gene expression profiling was conducted and 650 sperm-enriched genes were identified along with 258 oocyte-enriched genes and 508 germline-intrinsic genes.[36] When these genes were mapped to the *C. elegans* genome, the oocyte-enriched genes were found randomly distributed, but both germline-intrinsic and sperm-enriched genes were significantly under-represented on the X chromosome.

Evolutionary mechanisms influencing sex-chromosome gene content

From the preceding discussion, it is clear that sex chromosomes harbor a nonrandom assortment of genes. Both X and Y chromosomes are enriched for genes related to sex and reproduction; but the X is also enriched for genes involved in brain and skeletal muscle functions. Several evolutionary mechanisms may contribute to this phenomenon. Some mechanisms, such as regionally localized gene family growth[37] and the sharing of *cis*-acting regulatory elements by many genes,[38] must necessarily contribute to the nonrandom distribution of genes in the genome as a whole, including that seen in sex chromosomes. Other mechanisms arise from the unique properties of the sex chromosomes and are therefore specific to these chromosomes. Below, we will discuss four such sex-specific mechanisms.

Asexual degeneration

The heterogametic sex chromosome (i.e., the Y or the W) is, with rare exception, small and genetically impoverished

relative to both their homogametic counterparts (i.e., the X or the Z) and the autosomes. The question then arises as to how the reduction in size and the decay in gene function occurred. This topic has been well reviewed in the literature, and the consensus is that asexual degeneration results from the suppression of recombination on the heterogametic chromosome.[8,21,39–41]

Following the emergence of the sex-determining locus on the incipient mammalian sex chromosomes, recombination between neo-X and neo-Y might first become suppressed within a small circumscribed region immediately surrounding the sex-determining locus. This could be achieved either by progressive sequence divergence leading to impaired meiotic pairing and recombination in this region, or by chromosomal rearrangements of the region such as inversions. During subsequent evolution of the mammalian sex chromosomes, suppression of recombination between X and Y would spread out from the sex-determining locus to encompass progressively larger proportions of the chromosomes. Such expansions have been shown to occur in a block-by-block manner, perhaps as a result of large-scale inversions on the Y, where they resulted in the sudden suppression of recombination between Y and X within a large swath of chromosomal territory.[9] Given that large chromosomal rearrangements of the Y or of any chromosome are likely to be deleterious (because they compromise meiotic pairing, sometimes truncate genes, and can cause genic aneuploidy following recombination), it is puzzling why these inversion events should become fixed in a population. Possible explanations include genetic drift under small population size of the Y, or positive selection for certain alleles carried by the inversion-bearing chromosome (*i.e.*, genetic hitchhiking).[21]

Following the suppression of recombination, deleterious mutations accumulate in the NRY and cause this region to wither away (illustrated in Fig. 1A). Several hypotheses have been put forth to explain why harmful alleles amass in the absence of recombination. Among these are Muller's ratchet,[42,43] the Hill-Robertson effect,[44,45] genetic hitchhiking,[46] population size effect,[47] and background selection.[48,49] Muller's ratchet is predicated from the inability of a non-recombining region to regenerate its most-fit haplotypes. It postulates that, in the absence of recombination, the most-fit haplotype will be removed by deleterious mutations at a stochastic rate depending on population size. The outcome is functional decay of the region. The Hill-Robertson effect incorporates the concept of back mutations, but is largely similar to Muller's ratchet. Genetic hitchhiking occurs when deleterious mutations are pulled to fixation along linked, positively selected alleles. This may occur at a greater frequency on the NRY due to the complete absence of recombination. According to the argument of population size effect, the small population size of the Y is predicted to reduce the overall efficacy of selection in eliminating deleterious mutations. Finally, background selection leads to a further reduction in the effective population size of the Y chromosome, because selection against deleterious alleles removes a subset of the Y chromosomes from the population pool. While precise mechanisms may vary, all these hypotheses assume that most mutations are deleterious, and that only recombination is effective in recreating fit haplotypes from unfit ones.

While degeneration appears to be the predominant fate of NRY genes, there are those that escape this fate, at least for some period of time. One type of such genes are the NRY class 1 genes (Table 1), which are characterized by their involvement in critical housekeeping functions. These housekeepers can better resist the onslaught of NRY degeneration presumably because their functional preservation is more strongly favored by selection than is the case for other NRY genes. Another type of genes that escape NRY degeneration are those that have evolved male-specific functions, which are discussed in later sections.

Sexual antagonism

Sexual antagonism describes the situation where a gene is beneficial in one sex but is harmful in the other sex. Many traits associated with mating display are believed to be sexually antagonistic.[50] Most cited examples include the bright male coloration in guppies,[51] and the almost ridiculously large eye span in male stalk-eyed flies.[52] The genes that underlie these traits are considered to be sexually antagonistic because they benefit males by increasing sexual attractiveness and hence mating success (though they also increases predation), but harm females by increasing predation without enhancing attractiveness.

Sexually antagonistic alleles can and are located anywhere in the genome. In order for a sexually antagonistic allele to move to fixation, its positive effect in one sex must outweigh its negative effect in the other.[53] Alternatively, the allele must evolve a sex-restricted expression pattern.[54] This is not unusual and is often accomplished through the effects of sex hormones. This situation does, however, require additional modifiers to the genes that may or may not be easily accomplished.

There is reason to believe that selection is much more efficacious when sexually antagonistic genes are located on the sex chromosomes[54,55] (illustrated in Fig. 1B). If a sexually antagonistic gene is linked to one of the sex chromosomes, its presence in the sexes will be unequal. For a gene beneficial to females but harmful to males, its linkage to the X chromosome would effectively mean that this gene exists twice as often in its preferred sex. One would then predict that for a newly arisen mutation on the X that benefits females but harms males, it would go to fixation more readily than if the mutation occurred on an autosome. However, one needs to consider the caveat that if the male antagonistic effect of an X-linked allele is recessive, its hemizygous exposure in males might actually

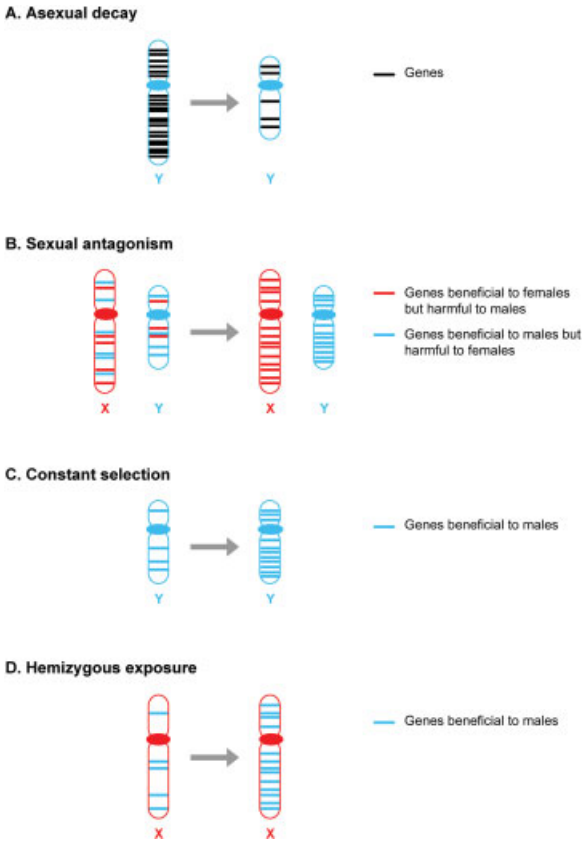

Figure 1. Effects of the four evolutionary forces on the sex chromosomes. **A**: Asexual decay results in a reduction in gene number and size of the Y chromosome. **B**: Sexual antagonism results in masculinization of the Y chromosome and feminization of the X chromosome. **C**: Constant selection predicts masculinization of the Y chromosome. **D**: Hemizygous exposure predicts some masculinization of the X chromosome.

exaggerate its deleterious impact on male fitness, which could impair (rather than enhance) its chance of fixation. So, how sexual antagonism affects gene content of the X chromosome may be rather complicated, and depend on the functional nature of the genes/mutations involved. For a gene beneficial to males but harmful to females, the effect of sex-chromosome linkage is much easier to predict. If such a gene is linked to the Y chromosome, it is always present in the preferred sex, a condition that undoubtedly offers an adaptive advantage than if the gene resided on an autosome.

The theory of sexual antagonism predicts that genes beneficial to one sex but harmful to the other would accumulate on sex chromosomes either by translocations from autosomal loci,[56] or by evolutionary modifications of preexisting sex chromosomal genes. Such a process has been experimentally modeled in *Drosophila*. In one such study, an autosomal dominant allele for eye color was used as a "pseudo-sex determining gene" i.e., only heterozygous females with the dominant eye color and homozygous males with the recessive eye color were allowed to reproduce.[57] This would predict that genes in tight linkage with the eye color gene would garner female beneficial mutations. After 29 generations of breeding, the fitness of heterozygous males and homozygous recessive females (i.e., sexes with opposite "pseudo-sex determining genotypes") were tested and, as expected, the males showed significantly reduced fitness while the females show a slight, but not statistically significant, increase in fitness. These experiments showed an accumulation of female-selected sexually antagonistic genes in linkage with the artificially introduced female sex-determining locus.

A similar experiment was conducted in which the male line specifically and faithfully transmitted a haploid genome.[58] The genome was selected in the male line for 41 generations and then transferred into otherwise wild-type males and females with the fitness effects measured. As expected, male-selected sexually antagonistic alleles had indeed accumulated, resulting in a net fitness increase for males and a decrease in females. An extension of this experiment was undertaken by isolating the X chromosome only and measuring its fitness effects in males and females.[59] These studies showed that the X contained 45% of the total fitness variation and 97% of the total sexually antagonistic fitness variation in the genome. Again a result consistent with theoretical predictions of sexual antagonism.

Contrary to the fly, little experimental evidence exists in mammals to support a strong presence of sexual antagonism. It has been noted, however, that, when a piece of the human Y chromosome is abnormally present in females, it causes a tumor of the ovary known as gonadoblastoma.[60] This observation has been interpreted by some as a manifestation of sexually antagonistic genes on the Y chromosome, though other interpretations cannot be excluded.

Constant selection

Genes residing on the heterogametic sex chromosome, being uniparentally inherited, are constantly under selective pressure in the context of the heterogametic sex. In the case of the Y chromosome, constant selection would drive any Y-linked male-beneficial alleles to fixation at rates faster than might occur on autosomes (illustrated in Fig. 1C). Further, there is reason to believe that selective pressure on male-specific genes is likely to be stronger than those found elsewhere.[61,62]

Unlike sexual antagonism, constant selection makes no assumptions about the effect of these genes on females. An allele beneficial to males is more likely to move to fixation on the Y chromosome because of the constant, unidirectional selection on it. This, coupled with the fact that males have a greater variability in reproductive success, is likely to result in the masculinization of the Y chromosome.

Genes involved in spermatogenesis or sperm competition may be the category of genes most likely to benefit from constant selection. Sperm competition, the race between millions of sperm to fertilize one or a few eggs, is a process of intense selection. This is especially true in polyandrous mating systems where sperm from one male has to compete for fertilization with sperm from one or more rival males. Many factors of sperm biology, including sperm number, sperm stamina, and the ability to manipulate the preference of eggs, have been suggested to be under strong sexual selection.[63] In the context of constant selection (and also hemizygous exposure as discussed in the next section), it is perhaps not surprising that the Y chromosome is highly enriched for spermatogenesis-related genes.

What may be somewhat surprising, however, is that genes traditionally believed to be under only weak or moderate sexual selection should also be found on the heterogametic chromosome. Genes controlling body weight dimorphism in Muscovy (*Cairina moschata*) and Pekin (*Anas platyrhynchos*) ducks,[64] sexually dimorphic developmental programs in white campion (*Silene latifolia*),[65] and egg size dimorphism in the American Kestral (*Falco sparverius*)[66] all reside on the heterogametic chromosome. While the evolutionary relationship between these sexual traits and the sex-chromosome linkage of their corresponding genes is unclear, it is worth noting that these genes are similar to reproduction-related genes on the heterogametic sex chromosome in that they are involved in highly sex-specific functions.

One caveat must be noted, however. The stochastic noise of genetic drift is greater on the Y relative to autosomes due to smaller effective population size (there is one Y chromosome for every four autosomes and three X chromosomes). It is argued, at least in theory, that small effective population size reduces the efficacy of selection and increases the role of random genetic drift in the fixation or extinction of alleles.[47] Without more detailed modeling, it remains to be seen how much additional advantage an allele must confer for it to have an overall greater likelihood of fixation on the Y relative to on an autosome. Despite this caveat, the argument of constant selection seems rather compelling in explaining the increase in sex and reproduction genes on the human Y chromosome.

Given that the X chromosome spends twice as much time in females as it does males, constant selection may also have an effect on the accumulation of female-beneficial genes on the X. However, this effect must be much weaker in comparison to the impact of constant selection on the Y chromosome.

Hemizygous exposure

Unlike the sexual antagonism and constant selection arguments, the hemizygous exposure argument is relevant only to the gene content of the homogametic sex chromosome. 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. By contrast, sexually antagonistic genes beneficial to the heterogametic sex should become fixed more readily on the heterogametic sex chromosome than on autosomes. The hemizygous exposure argument postulates, somewhat counter-intuitively, that genes beneficial to the heterogametic sex may also have a tendency to accumulate on the homogametic sex chromosome (illustrated in Fig. 1D).

This argument reasons that alleles beneficial to the heterogametic sex are likely to become fixed on the homogametic sex chromosome as a result of their being exposed (i.e., hemizygous) in the heterogametic sex. For dominant alleles, this is irrelevant. But if the allele is recessive, then its hemizygous exposure in males should allow selection to operate more effectively in males than females.[53] Similar to the constant selection argument, genes benefiting from hemizygous exposure can include, but are not limited to, sexually antagonistic genes. Much of the work done on sexual antagonism implicitly bases the predicted masculinization of the X chromosome on this process,[54] and while indeed it may be that many of these recessive alleles beneficial to males are also harmful to females, they need not be for the mechanism to operate. Indeed any mutations that confers a selective advantage to the heterogametic sex regardless of its effect in the homogametic sex is likely to benefit from hemizygous exposure if they reside on the homogametic chromosome, provided that such mutations are recessive.

It has already been noted that the mammalian X chromosome appears to harbor more genes involved in early stages of spermatogenesis than expected.[26] The authors offered two hypotheses for their finding: sex-chromosome meiotic drive or sexual antagonism. The former cannot be ruled out and indeed sex chromosome-based meiotic drive has been observed in the mouse.[67] The sexual antagonism argument by the authors, however, can in fact be better characterized as hemizygous exposure—i.e., the accumulation of spermatogenic genes on the X chromosome may have depended critically on the hemizygous nature of recessive male-beneficial mutations on the X chromosome of males.

There are several other examples of genes uniquely beneficial to the heterogametic sex, yet residing on the homogametic sex chromosome. Male courtship songs in *Drosophila* species and in some crickets (*Laupala*) appear to be X-linked,[68] as does eye-span length, a sexually selected trait in stalk-eyed flies (*Cyrtodiopsis dalmanni*),[52] and a coloration mimicry seen only in the female tiger swallowtail butterfly (*Papilio glaucus*).[69] These situations are not adequately explained by previous prevailing theories such as sexual antagonism, but may be understood, at least in part, through the hemizygous exposure argument.

Again, the smaller population size of the X chromosome may increase genetic drift and more modeling is required to

establish selective levels necessary to drive alleles to fixation. But it seems likely that this force is at work in nature.

Implications for human and mammalian evolution

It has been repeatedly suggested that many of the uniquely human traits are the result of runaway sexual selection.[28] This hypothesis gains some credence from the observation that genes underlying brain function, a biological domain that most saliently distinguishes humans from other species, appear to exist in excess on the human X chromosome (where sexual selection has likely had some impact). Below, we discuss the possibility that the evolution of sex-chromosome gene content may be intimately tied to the evolution of certain human-specific traits.

How did a preponderance of brain-related genes end up on the human X? One possibility is that it happened by chance, and is unrelated to the unique properties of the sex chromosomes. The other possibility is the existence of selective mechanisms unique to the sex chromosomes. Two such mechanisms discussed in this paper, sexual antagonism and hemizygous exposure, are perhaps relevant. Brain size has previously been suggested to be a sexually antagonistic trait with females realizing less benefits than males as a result of difficulties in birthing babies with large heads.[28] However, this would suggest an accumulation of brain-related genes on the Y rather than the X chromosome. Furthermore, in order for brain-related genes to accumulate on the X by sexual antagonism, they would have to benefit females and harm males. There is obviously no empirical or theoretical evidence to support this. Hence, as tantalizing as the sexual antagonism argument may appear at first glance, it cannot logically account for the enrichment of brain-related genes on the human X chromosome.

The hemizygous exposure mechanism is perhaps a more plausible explanation. But in order for this to be the case, the influence of selection upon brain-related genes on the X would have to be greater in males than females. Its potentially contentious social implications aside, is such a view scientifically feasible? There are several reasons to believe that this may be the case. First, reproductive skew, the mechanism underlying selection, is much greater in males than in females.[70–72] It is therefore not unreasonable to imagine that larger brain (and hence greater cognitive capacity) has allowed males to achieve higher levels of reproductive success compared to their small-brained brethren than it has in females. Second, regardless of whether larger brain confers greater reproductive advantage in males or females, recessive beneficial mutations on the X chromosome offer greater selective advantage to males, as predicted by the hemizygous exposure argument. Third, the selection for larger brain need not even be the same as selection for greater cognitive abilities. Sexual selection in which females prefer males with larger heads, and in which greater cognitive abilities were merely a secondary benefit, could also produce the observed effect. In this context, it is interesting to note that many primates, including humans, show a preference for neotenous appearance. Such a preference could conceivable underlie the sexual selection for larger brain.[50]

The hemizygous exposure argument does not necessarily imply a difference in male and female brain size or cognitive abilities. What it does suggest is that beneficial recessive alleles would more easily reach intermediate frequency and then progress to fixation if on the X chromosome than if on an autosome. Hence, if selection for a larger brain was intense enough during human evolution and recessive mutations were the substrate upon which this selection acted, recessive X-linked mutations that enlarged the brain could be strongly favored by selection due to hemizygous exposure of these mutations in males even if larger brain doesn't necessarily benefit males more than it does females. Once these recessive mutations reached fixation in the population, they might well benefit males and females equally by conferring larger brain size (and presumably greater cognitive abilities) to both sexes. The result is an enrichment of brain-related genes on the human X chromosome regardless of whether these genes play a role in brain differences between the sexes.

All of the above hypotheses are far from certain, however. While it seems clear that there is an unexpected excess of brain-related genes on the X chromosome, to explain it will require a greater understanding of how the human brain evolved and what genes and alleles were involved. Surveys of sex-chromosome gene content in other organisms will shed light on whether the abundance of brain-related genes on the X is mammalian-, primate-, or human-specific. Recent studies of mice in which *SRY* has been experimentally translocated onto an autosome have shown, however, that sex-chromosome genes indeed contribute directly to sex differences found in the brain apart from their indirect effects through gonadal hormones.[73]

A less controversial argument, though equally unproven and even less considered, may be found in the excess of skeletal muscle genes on the human X chromosome. That alterations to human musculature would disproportionately benefit males may be more intuitive and palatable. This benefit would allow for hemizygous exposure to act more effectively to enrich muscle-related genes on the X chromosome. But as with brain-related genes, this argument suffers from the uncertainty as to whether females have indeed benefited less from increased musculature than have males. It is also unclear how the skeletal muscle genes found on the human X chromosome would translate into phenotypes in musculature at all.

Regarding male reproduction genes on the X chromosome, a contradiction can be found between mammals where these

genes appear to be over-represented,[25,26] and *Drosophila* and *C. elegans* where they are under-represented.[33,36] The contradiction can be explained by the differing extents to which various evolutionary mechanisms are at play in one versus another species. For example, hemizygous exposure might have had a great impact in mammals, while sexual antagonism might have impinged more strongly in *Drosophila* and *C. elegans*. But in truth, this contradiction can also be explained by biological rather than evolutionary mechanisms.[74] The excess male-beneficial genes on the mammalian X are involved in early spermatogenesis,[26] a process taking place prior to X inactivation in male germ cells. By contrast, the *Drosophila* and *C. elegans* studies both used cells of late spermatogenesis, where the X may have already been inactivated in the male germline. Recent understandings of the situation in fact combine these two observations, suggesting that sexual antagonism and X inactivation may combine to demasculinize the X chromosome by redistributing late spermatogenic genes to the autosomes.[75]

The major mammalian radiation appears to have coincided with a large autosomal translocation onto the sex chromosomes 80–130 million years ago.[76] If sex-chromosome genes have indeed played prominent roles in evolutionary adaptation, then could this translocation have provided the genetic material required for the ensuring flurry of speciation events? How was the mammalian adaptive landscape shaped by the seemingly random choice of which autosomes would become the sex chromosomes? Further, could the adaptive landscape have been different for birds or snakes because their nascent sex chromosomes harbored different genes or because of their ZZ:ZW mechanism of sex determination? These are intriguing questions for future investigations.

It has recently been suggested that the ZZ:ZW sex-determination system is more conducive to sexual selection than the XX:XY system.[77] This has been suggested by the extensive diversity of male ornamentation traits found in birds.[78] While modeling remains incomplete, a ZZ:ZW system seems to allow for greater variation to accumulate on the homogametic sex chromosome as well as limiting the rate of degeneration of the heterogametic sex chromosome. Higher male mutation rates[72] offer greater amounts of raw material for selection to act upon the Z chromosome; and the slower female mutation rates retard degeneration of the W chromosome, thus allowing constant selection a greater window to work. This remains an area of speculation; however, it is likely that the evolutionary processes shaping the Z and W sex chromosomes may differ in certain systematic ways from the processes shaping the X and Y chromosomes.

Conclusion

Sex chromosomes are clearly different from autosomes. In addition to differences in physical appearance, population size and evolutionary history, they show unique patterns of gene content. The human Y chromosome has lost much of its material and retained only a few genes, many of them playing a role in spermatogenesis.[17] The X chromosome has a similar size and number of genes compared to the autosomes, but its genes also show an interesting pattern of functional coherence, with greater than expected numbers of genes involved in sex and reproduction, brain-related functions, and skeletal muscle expression.[25–28,32]

Four different hypotheses have contributed to our understanding of the forces that may have affected the sex-chromosome gene content (summarized in Table 2). Asexual decay has resulted in the loss of the genes and the shrinkage in size of the Y chromosome. Sexual antagonism and constant selection may have helped the X and Y chromosomes take on their sex-specific features. And finally, hemizygous exposure may have provided the means to explain the curious masculinization of the X chromosome.

It is not immediately reconcilable that spermatogenesis genes should be overly abundant on the X chromosome. Nor is

Table 2. Four evolutionary forces affecting gene content of the sex chromosomes

Evolutionary force	Substrate of action	Effect on X chromosome	Effect on Y chromosome
Asexual decay	All NRY genes	Dosage compensation (as an adaptive response to Y degeneration)	Degeneration of most genes, loss of chromosome size
Sexual antagonism	Genes or mutant alleles with opposing fitness effects on the two sexes (i.e., beneficial in one sex but harmful in the other)	Accumulation and functional enhancement of female-beneficial genes	Accumulation and functional enhancement of male-beneficial genes
Constant selection	Mutant alleles on the Y chromosome that are beneficial to males	Not applicable	Accumulation and functional enhancement of male-beneficial genes
Hemizygous exposure	Recessive mutant alleles on the X chromosome that are beneficial to males	Accumulation and functional enhancement of male-beneficial genes	Not applicable

it intuitively obvious why any class of genes should be over-represented on the X chromosome if this pattern is not observed on autosomes. That genes should remain on the Y chromosome is equally puzzling given that such a large number have apparently been lost through degradation. Sexual antagonism is commonly proposed to explain these phenomena, but it may not be the only, or indeed the most likely, explanation. The constant selection and hemizygous exposure arguments (and perhaps still other unexplored arguments) must also be considered as forces acting upon sex-chromosome gene content. The extent to which these forces may shape the sex chromosomes is still an unresolved topic of ongoing research. It will be of interest to see if the patterns of sex chromosomal genes seen in a few species will hold true in many more species, and what, if any, additional patterns will be found.

In sum, the studies of sex chromosomes, especially in relation to their unusual gene content, have offered and will continue to offer important insights into the evolutionary forces shaping genes and genomes, and may even shed some light on the evolution of our own species.

References

1. Pal C, Hurst LD. Evidence for co-evolution of gene order and recombination rate. Nat Genet 2003;33:392–395.
2. Korpelainen H. Sex ratios and conditions required for environmental sex determination in animals. Biol Rev Camb Philos Soc 1990;65:147–184.
3. Bull JJ. Evolution of Sex Determining Mechanisms. Calif.: Menlo Park; 1983.
4. de Almeida Toledo LF, Foresti F. Morphologically differentiated sex chromosomes in neotropical freshwater fish. Genetica 2001;111:91–100.
5. Bull JJ, Bulmer MG. The Evolution of XY Females in Mammals. Heredity 1981;47:347–365.
6. Volff JN, Schartl M. Variability of genetic sex determination in poeciliid fishes. Genetica 2001;111:101–110.
7. Wilkins AS. Moving Up the Heirarchy-A Hypothesis on the Evolution of a Genetic Sex Determination Pathway. Bioessays 1995;17:71–77.
8. Lahn BT, Pearson NM, Jegalian K. The human Y chromosome, in the light of evolution. Nat Rev Genet 2001;2:207–216.
9. Lahn BT, Page DC. Four evolutionary strata on the human X chromosome. Science 1999;286:964–967.
10. Stevanovic M, Lovell-Badge R, Collignon J, Goodfellow PN. SOX3 is an X-linked gene related to SRY. Hum Mol Genet 1993;2:2013–2018.
11. Foster JW, Graves JA. An SRY-related sequence on the marsupial X chromosome: implications for the evolution of the mammalian testis-determining gene. Proc Natl Acad Sci USA 1994;91:1927–1931.
12. Marshall Graves JA, Shetty S. Sex from W to Z: evolution of vertebrate sex chromosomes and sex determining genes. J Exp Zool 2001;290: 449–462.
13. Smith CA, McClive PJ, Western PS, Reed KJ, Sinclair AH. Conservation of a sex-determining gene. Nature 1999;402:601–602.
14. Nanda I, et al. Conserved synteny between the chicken Z sex chromosome and human chromosome 9 includes the male regulatory gene DMRT1: a comparative (re)view on avian sex determination. Cytogenet Cell Genet 2000;89:67–78.
15. Hurst LD, Randerson JP. An eXceptional chromosome. Trends Genet 1999;15:383–385.
16. Ohno S. Sex chromosomes and sex-linked genes. Berlin: Springer Verlag; 1967.
17. Delbridge ML, Graves JA. Mammalian Y chromosome evolution and the male-specific functions of Y chromosome-borne genes. Rev Reprod 1999;4:101–109.
18. Graves JA. Evolution of the mammalian Y chromosome and sex-determining genes. J Exp Zool 1998;281:472–481.
19. Lahn BT, Page DC. Functional coherence of the human Y chromosome. Science 1997;278:675–680.
20. Skaletsky H, et al. The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. Nature 2003;423:825–837.
21. Rice WR. Evolution of the Y sex chromosome in animals. BioScience 1996;46:331–343.
22. Charlesworth B. Genome analysis: More Drosophila Y chromosome genes. Curr Biol 2001;11:R182–R184.
23. Carvalho AB, Dobo BA, Vibranovski MD, Clark AG. Identification of five new genes on the Y chromosome of Drosophila melanogaster. Proc Natl Acad Sci USA 2001;98:13225–13230.
24. Hurst LD. Evolutionary genomics. Sex and the X. Nature 2001;411:149–150.
25. Saifi GM, Chandra HS. An apparent excess of sex- and reproduction-related genes on the human X chromosome. Proc R Soc Lond B Biol Sci 1999;266:203–209.
26. Wang PJ, McCarrey JR, Yang F, Page DC. An abundance of X-linked genes expressed in spermatogonia. Nat Genet 2001;27:422–426.
27. Qiu P, Benbow L, Liu S, Greene JR, Wang L. Analysis of a human brain transcriptome map. BMC Genomics 2002; 3.
28. Zechner U, Wilda M, Kehrer-Sawatzki H, Vogel W, Fundele R, Hameister H. A high density of X-linked genes for general cognitive ability: a run-away process shaping human evolution? Trends Genet 2001;17:697–701.
29. Herbst DS, Miller JR. Nonspecific X-linked mental retardation II: the frequency in British Columbia. Am J Med Genet 1980;7:461–469.
30. Hedges LV, Nowell A. Sex differences in mental test scores, variability, and numbers of high- scoring individuals. Science 1995;269:41–45.
31. Wilda M, Bachner D, Zechner U, Kehrer-Sawatzki H, Vogel W, Hameister H. Do the constraints of human speciation cause expression of the same set of genes in brain, testis, and placenta? Cytogenet Cell Genet 2000; 91:300–302.
32. Bortoluzzi S, et al. A comprehensive, high-resolution genomic transcript map of human skeletal muscle. Genome Res 1998;8:817–825.
33. Parisi M, Nuttall R, Naiman D, Bouffard G, Malley J, Andrews J, Eastman S, Oliver B. Paucity of Genes on the Drosophila X-Chromosome Showing Male-Biased Expression. Science 2003;299:697–700.
34. Boutanaev AM, Kalmykova AI, Shevelyov YY, Nurminsky DI. Large clusters of co-expressed genes in the Drosophila genome. Nature 2002; 420:666–669.
35. Chasnov JR, Chow KL. Why Are There Males in the Hermaphroditic Species Caenorhabditis elegans? Genetics 2002;160:983–994.
36. Reinke V, et al. A global profile of germline gene expression in C. elegans. Mol Cell 2000;6:605–616.
37. Glusman G, Yanai I, Rubin I, Lancet D. The Complete Human Olfactory Subgenome. Genome Res 2001;11:685–702.
38. Lawrence JG. Shared Strategies in Gene Organization among Prokaryotes and Eukaryotes. Cell 2002;110:407–413.
39. Charlesworth B, Charlesworth D. The degeneration of Y chromosomes. Philos Trans R Soc Lond B Biol Sci 2000;355:1563–1572.
40. Graves JA. The origin and function of the mammalian Y chromosome and Y-borne genes–an evolving understanding. Bioessays 1995;17: 311–320.
41. Steinemann M, Steinemann S. Common mechanisms of Y chromosome evolution. Genetica 2000;109:105–111.
42. Gordo I, Charlesworth B. On the speed of Muller's ratchet. Genetics 2000;156:2137–2140.
43. Muller HJ. The relation of recombination to mutational advance. Mutat Res 1964;1:2–9.
44. Hill WG, Robertson A. The effect of linkage on limits to artificial selection. Genet Res 1966;8:269–294.
45. McVean GAT, Charlesworth B. The effects of Hill-Robertson interference between weakly selected mutations on patterns of molecular evolution and variation. Genetics 2000;155:929–944.
46. Barton NH, Charlesworth B. Why sex and recombination? Science 1998;281(5385):1986–1990.
47. Ohta T. Near-neutrality in evolution of genes and gene regulation. Proc Natl Acad Sci USA 2002;99:16134–16137.

48. Charlesworth B. The evolution of chromosomal sex determination and dosage compensation. Curr Biol 1996;6:149–162.
49. Gordo I, Charlesworth B. The speed of Muller's ratchet with background selection, and the degeneration of Y chromosomes. Genet Res 2001;78: 149–161.
50. Gavrilets S, Arnqvist G, Friberg U. The evolution of female mate choice by sexual conflict. Proc R Soc Lond B Biol Sci 2001;268: 531–539.
51. Brooks R. Negative genetic correlation between male sexual attractiveness and survival. Nature 2000;406:67–70.
52. Wolfenbarger LL, Wilkinson GS. Sex-linked expression of a sexually selected trait in the stalk-eyed fly, Cyrtodiopsis dalmanni. Evolution Int J Org Evolution 2001;55:103–110.
53. Charlesworth B, Coyne JA, Barton NH. The Relative Rates of Evolution of Sex Chromosomes and Autosomes. Am Nat 1987;130: 113–146.
54. Rice WR. Sex chromosomes and the evolution of sexual dimorphism. Evolution 1984;38:735–742.
55. Fisher RA. The evolution of dominance. Biol Rev 1931;6:345–368.
56. Charlesworth D, Charlesworth B. Sex differences in fitness and selection for centric fusions between sex-chromosomes and autosomes. Genet Res 1980;35:205–214.
57. Rice WR. Sexually antagonistic genes: experimental evidence. Science 1992;256:1436–1439.
58. Rice WR. Male fitness increases when females are eliminated from gene pool: implications for the Y chromosome. Proc Natl Acad Sci USA 1998; 95:6217–6221.
59. Gibson JR, Chippindale AK, Rice WR. The X chromosome is a hot spot for sexually antagonistic fitness variation. Proc R Soc Lond B Biol Sci 2002;269:499–505.
60. Tsuchiya K, Reijo R, Page DC, Disteche CM. Gonadoblastoma: molecular definition of the susceptibility region on the Y chromosome. Am J Hum Genet 1995;57:1400–1407.
61. Ting CT, Tsaur SC, Wu ML, Wu CI. A rapidly evolving homeobox at the site of a hybrid sterility gene. Science 1998;282:1501–1504.
62. Wyckoff GJ, Wang W, Wu CI. Rapid evolution of male reproductive genes in the descent of man. Nature 2000;403:304–309.
63. Pizzari T, Birkhead TR. The sexually-selected sperm hypothesis: sex-biased inheritance and sexual antagonism. Biol Rev Camb Philos Soc 2002;77:183–209.
64. Tai C, Rouvier R. Crossbreeding effect on sexual dimorphism of body weight in intergeneric hybrids obtained between Muscovy and Pekin duck. Genet Sel Evol 1998;30:163–170.
65. Moneger F, Barbacar N, Negrutiu I. Dioecious Silene at the X-road: the reasons Y. Sex. Plant Reprod 2000;12:245–249.
66. Anderson DJ, Reeve J, Bird DM. Sexually dimorphic eggs, nestling growth and sibling competition in American Kestrels Falco sparverius. Funct Ecol 1997;11:331–335.
67. de La Casa-Esperon E, Loredo-Osti JC, Pardo-Manuel de Villena F, Briscoe TL, Malette JM, Vaughan JE, Morgan K, Sapienza C. X chromosome effect on maternal recombination and meiotic drive in the mouse. Genetics 2002;161:1651–1659.
68. Shaw KL. Polygenic inheritance of a behavioral phenotype: interspecific genetics of song in the Hawaiian cricket genus Laupala. Evolution 1996;50:256–266.
69. Scriber JM, Hagen RH, Lederhouse RC. Genetics of mimicry in the tiger swallowtail butterflies Papilio glaucus and P-canadensis (lepidoptera: Papilionidae). Evolution 1996;50:222–236.
70. Bateman AJ. Intra-Sexual Selection in Drosophila. Heredity 1948;2:349–368.
71. Clutton-Brock TH, Vincent ACJ. Sexual selection and the potential reproductive rates of males and females. Nature 1991;351:58–60.
72. Makova KD, Li WH. Strong male-driven evolution of DNA sequences in humans and apes. Nature 2002;416:624–626.
73. De Vries GJ, Rissman EF, Simerly RB, Yang LY, Scordalakes EM, Auger CJ, Swain A, Lovell-Badge R, Burgoyne PS, Arnold AP. A model system for study of sex chromosome effects of sexually dimorphic neural and behavioral traits. J Neuroscience 2002;22:9005–9014.
74. Betran E, Thornton K, Long M. Retroposed New Genes Out of the X in Drosophila. Genome Res 2002;12:1854–1859.
75. Wu CI, Xu EY. Sexual antagonism and X inactivation- the SAXI hypothesis. Trends Genet 2003;19:243–247.
76. Waters PD, Duffy B, Frost CJ, Delbridge ML, Graves JA. The human Y chromosome derives largely from a single autosomal region added to the sex chromosomes 80-130 million years ago. Cytogenet Cell Genet 2001;92:74–79.
77. Reeve HK, Pfennig DW. Genetic biases for showy males: Are some genetic systems especially conducive to sexual selection? PNAS 2003; 100:1089–1094.
78. Darwin C. The Descent of Man and Selection in Relation to Sex. London: John Murray; 1874.