The evolutionary causes and consequences of sex-biased gene expression

John Parsch and Hans Ellegren

Abstract | Females and males often differ extensively in their physical traits. This sexual dimorphism is largely caused by differences in gene expression. Recent advances in genomics, such as RNA sequencing (RNA-seq), have revealed the nature and extent of sex-biased gene expression in diverse species. Here we highlight new findings regarding the causes of sex-biased expression, including sexual antagonism and incomplete dosage compensation. We also discuss how sex-biased expression can accelerate the evolution of sex-linked genes.

It is common knowledge that the females and males of a species differ in many morphological, physiological and behavioural characteristics. Indeed, the presence of two sexes typically constitutes the most extreme phenotypic variation seen within species. However, aside from sex-specific genetic elements that contain very few genes (such as the Y chromosome of mammals or the W chromosome of birds), females and males share a common genome. How then can so many traits vary between the sexes?

In the past decade, genome-wide analyses of gene expression have revealed that lying beneath the extensive phenotypic divergence between the sexes there is an equally impressive amount of gene expression divergence. The genes that differ in expression between females and males are known as sex-biased genes, and in principle their evolution should be subject to the same forces that govern the evolution of phenotypic characters: namely, natural selection, sexual selection and genetic drift. Additionally, as conflicts regarding the expression level of genes in the two sexes must be prevalent, the constraints imposed by sexual antagonism are also likely to influence the evolution of sex-biased genes.

In 2007, we reviewed the status of evolutionary studies of sex-biased genes and sex-biased gene expression[1], which were then still in their infancy. Since then, technological developments have led to a dramatic increase in relevant data. This has been fuelled by high-throughput sequencing methods that allow comparative genomic studies between species and allow population genomic studies within species. Similarly, high-throughput RNA sequencing (RNA-seq) and microarray analyses have allowed gene expression differences between the sexes to be studied in a wide range of species and in multiple tissues within an organism.

The goal of this Progress article is to highlight recent discoveries and to describe how they extend or revise previous concepts. We begin with the evolutionary causes of sex-biased gene expression and how forces such as sexual antagonism and mechanisms such as gene duplication may contribute to the observed patterns. We also discuss the contribution of sex-chromosome-specific processes, such as dosage compensation, to sex-biased gene expression. We then turn to the evolutionary consequences of sex-biased gene expression and how the interplay between sex-specific selection and chromosomal location affects the evolutionary rate of genes and proteins.

Causes of sex-biased expression

Sexual antagonism. The idea that sexual antagonism may underlie the evolution of sex-biased gene expression is conceptually uncontroversial (FIG. 1), but this does not necessarily mean that all sex-biased genes are or have been sexually antagonistic. Unfortunately, although many phenotypic aspects of sexual conflict are well understood[2], the genetic basis of sexual antagonism remains something of a black box. Experiments using *Drosophila melanogaster* have demonstrated that different genetic backgrounds can have opposing effects on male and female fitness[3]; however, the identity, number and location of sexually antagonistic genes are largely unknown. As a consequence, there is currently poor awareness of the extent to which intralocus sexual conflict — either past or present — explains sex-biased gene expression.

However, some important progress has been made through a recent study of hemiclonal lines of *D. melanogaster* (that is, haploid clones that can be expressed as either males or females)[4]. This study found that 8% of the genes in the genome show segregating expression variation with opposite fitness effects in females and males, reflecting current sexual antagonism. The observed proportion of sexually antagonistic genes is much less than the proportion of sex-biased genes in the genome, which could have at least three explanations. First, in this study[4], only a single aspect of fitness was measured — namely, the reproductive success of adult flies under laboratory conditions — suggesting that the observed proportion of sexually antagonistic genes is greatly underestimated. Many more genes may display sexually antagonistic expression for other fitness components and under natural conditions. Second, the sex-biased expression that is observed at present may reflect resolved rather than current conflicts. Third, many genes with sex-biased expression may not now nor ever have exhibited sexual antagonism. For this reason, caution should be taken when using sex-biased expression as a basis for the identification of sexually antagonistic genes. Indeed, the above study found that unbiased genes can also show sexually antagonistic variation in expression. Similarly, there is not a strong concordance between mutations in sex-biased genes and sex-specific phenotypic effects[5]. Both of these findings highlight the uncertain

relationship between sexual antagonism and sex-biased expression. Despite these unresolved issues, an important implication of the demonstration of segregating variation at sexually antagonistic genes is that sexual conflict can contribute to the maintenance of genetic diversity in the face of selection.

Gene duplication. Sexual conflict means that the two sexes have different fitness optima. The resulting selection pressures may therefore lead to suboptimal gene expression levels in both sexes (FIG. 1). One solution to this problem is the evolution of sex-biased expression mediated by *cis*-regulatory changes or *trans*-regulatory changes. A second solution is the partitioning of a gene's coding sequence into alternatively spliced transcript isoforms that differ between females and males[6,7]. A third solution is gene duplication, in which expression of the parental gene copy may remain unchanged, whereas the new copy can evolve sex-specific expression. Indirect evidence for this process being important in the generation of sex-biased gene expression has been accumulated in recent years[8–11]. Furthermore, as elegantly demonstrated by two recent studies[12,13], gene duplication provides a means for new sex-specific networks to evolve in which the new gene copy regulates a cascade of downstream genes. In one case, the retroduplication of an unbiased *Drosophila* housekeeping gene produced a new gene copy that evolved male-biased (testis) expression and now has an important functional role in determining male fecundity[12]. A similar case has been described in the mouse genus (*Mus*), wherein the recently derived Y-linked gene Sycp3-like Y-linked (*Sly*) interacts with two related X-linked genes, *Slx* and *Slxl1*, in an antagonistic fashion to regulate the expression of a suite of genes in spermatids and to influence male fertility[13].

Dosage compensation. Although the sex chromosomes differ in dosage between males and females, the expression of sex-linked genes is typically equalized between the sexes through the well-known process of dosage compensation. For this reason, the commonly observed enrichment of female-biased genes on the X chromosome of well-studied XY systems, such as mammals and *Drosophila* spp., has been attributed to factors other than gene dosage[14–17]. However, the situation appears to be different in ZW taxa. Following the initial observation that chickens (which are a ZW taxon) lack global dosage compensation[18,19], it has been shown that other birds, as well as other ZW systems (including silkworms[20] and the trematode parasite *Schistosoma mansoni*[21]), also lack general sex-chromosome dosage compensation. In all of these cases, there is an over-representation of male-biased genes on the Z chromosome[22,23], a finding that is consistent with gene dosage (FIG. 2). This is intriguing because it seems unlikely that the great majority of sex-linked genes in female heterogametic systems would benefit from male-biased expression; future efforts should be put into explaining this unexpected situation. Moreover, new data indicate that this phenomenon is not limited to female heterogametic taxa: the threespine stickleback *Gasterosteus aculeatus*[24] and the flour beetle *Tribolium castaneum*[25], which are both male heterogametic, have large excesses of female-biased genes on the X chromosome. In the case of the stickleback, this appears to result from an absence of chromosomal dosage compensation, which is analogous to what is seen in female heterogametic taxa. In the case of the flour beetle, it appears that a mechanism has evolved to upregulate the expression of X-linked genes[25]. However, this upregulation occurs in both sexes. In males, it balances the expression of X-linked and autosomal genes, whereas in females it leads to widespread overexpression of X-linked genes.

In *D. melanogaster*, which is well-known to show dosage compensation through upregulation of X-linked genes in male somatic cells, there is current controversy regarding whether dosage compensation also occurs in the male germ line[26,27]. A lack of dosage compensation could contribute to the paucity of male-biased genes on the X chromosome that is observed when whole bodies or dissected gonads are compared between the sexes[27]. Consistent with this hypothesis, it has recently been shown that after computationally adjusting expression values of X-linked genes in a manner consistent with gene dosage there is no longer a significant deficit of male-biased genes on the X chromosome[28]. Even in somatic tissues, it appears that dosage compensation is not uniform across the X chromosome. RNA-seq analyses of the head and brain have revealed a significant excess of male-biased genes on the X chromosome relative to the autosomes[29,30]. These male-biased genes tend to be located near binding sites for the dosage compensation complex (DCC) proteins. Thus, it is possible that their male-biased expression is a result of 'over-compensation' of genes in close proximity to DCC binding sites. Taken together, recent transcriptomic studies from a diverse range of species and tissues suggest that incomplete or imperfect dosage compensation may be responsible for a much greater proportion of sex-biased gene expression than was previously thought.

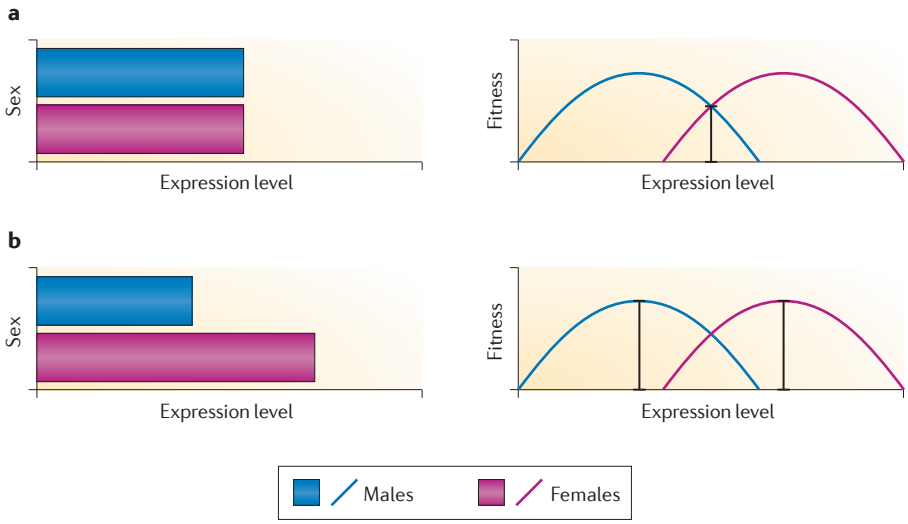

Figure 1 | **Sex-biased expression and differential fitness of males and females.** The left panel shows the expression levels in males and females when there is no sex-biased expression (**a**) and when there is sex-biased expression (**b**). The right panel shows the respective fitness distributions for males and females in relation to the level of gene expression. The black bars indicate the fitness of each sex, given the expression levels shown on the left. When there is no sex bias in gene expression, fitness is suboptimal for both sexes. With sex-biased expression, each sex comes closer to its fitness optimum.

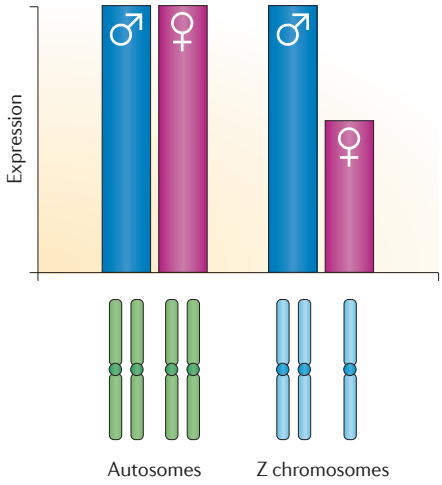

Figure 2 | **Male-biased expression of Z-linked genes.** In female heterogametic taxa, the presence of two Z chromosomes in males, but only one in females, leads to widespread male-biased expression of Z-linked genes.

Expression of sex-limited chromosomes. For genes that have a beneficial function to the heterogametic sex, but for which expression is deleterious to the homogametic sex, a location on the sex-limited chromosome (that is, Y or W) might be seen as the optimal genomic solution. However, genes on sex-limited chromosomes are sensitive to the degenerative forces that follow from the absence of recombination and a reduction in effective population size (N_e), which introduces a trade-off. This may explain why the Y chromosome of flies and mammals contains only a handful of genes that are essential for male fertility; most genes of this type are located elsewhere in the genome. Nonetheless, it is evident from recent experiments in *D. melanogaster* that Y chromosomes can have profound effects on sex-biased expression patterns of autosomal and X-linked genes. These have shown that haplotypic variation on the Y chromosome correlates with expression levels of male-biased genes located elsewhere in the genome[31]. Although the mechanism responsible for the effect of the Y chromosome on gene expression is not fully understood, it appears to be caused by non-genic elements of heterochromatin that influence the chromatin structure of other chromosomes and not by the Y-linked genes themselves[32]. Interestingly, variation in expression caused by the Y chromosome can have important phenotypic effects that may be relevant for adaptation[31]. In mammals, the familiar example of the sex-determining region of Y (*SRY*) gene on the Y chromosome nicely demonstrates how a cascade of sex-biased expression can be triggered by a single sex-limited gene[33]. Examples of targets for SRY include the autosomal SRY box containing gene 9 (*SOX9*) and anti-Müllerian hormone (*AMH*) genes.

Consequences of sex-biased expression

Rapid evolution of sex-biased genes. It is commonly observed that proteins encoded by sex-biased genes, especially male-biased genes, show greater amino acid sequence divergence between species than those encoded by genes with unbiased expression[1]. Typically, such evolutionary rate comparisons define sex-biased genes as those genes that differ in expression between adult samples of whole animals, including reproductive tissues. As might be expected, the number of sex-biased genes is greatest in such samples[14,15,34,35]. However, a gene's sex bias is not a fixed property but can vary among tissues or change over the course of development[15,34,35]. Thus, it is possible that the rapid evolution of sex-biased genes is not necessarily a result of their sex-biased expression but may be a result of another correlated feature, such as expression breadth (that is, the number of different tissues in which the gene is expressed). Indeed, many sex-biased genes tend to have a low expression breadth (often restricted to the testes or ovaries), and it is known that genes with tissue-specific expression tend to evolve faster than those with a high expression breadth[36]. Similarly, the evolutionary rate of sex-biased genes may be accelerated by a reduction in purifying selection, particularly if selection occurs in only one sex[37]. In *Drosophila* spp., male-biased genes consistently show faster rates of protein evolution than do female-biased or unbiased genes, but male-biased genes also show the least expression breadth[15,16]. This raises the possibility that increased pleiotropy due to expression in more tissue types limits the rate of evolution of female-biased and unbiased genes. Despite this, it has been shown that sex-biased genes expressed only in sex-limited reproductive tissues evolve faster than unbiased genes that are expressed only in a single, non-reproductive tissue[38,39]. This finding suggests that sex-specific effects on reproduction drive the rapid evolution of sex-biased genes; this is consistent with the generally observed pattern of accelerated evolution of genes with a known reproductive function[36,40].

Sex bias and the 'faster-X' effect. Because the X chromosome is hemizygous in males, beneficial mutations that are recessive have a greater probability of fixation when they are X-linked[41]. This is expected to lead to a 'faster-X' effect, in which the rate of evolution of the X chromosome is greater than that of the autosomes. An analogous 'faster-Z' effect is expected in ZW taxa. However, in addition to the degree of dominance of beneficial mutations, the extent of the faster-X effect and its underlying causes

Glossary

Cis-regulatory changes
Changes in gene regulatory sequences, such as promoters and enhancers, that alter the expression of genes located nearby on the same chromosome.

Effective population size
(N_e). An idealized description of the number of breeding individuals in a population over many generations. N_e is usually much smaller than the current census population size. As N_e increases, the influence of natural selection becomes greater, whereas the influence of genetic drift is diminished.

Genetic drift
Stochastic variation in allele frequency in a population across generations. The effect of genetic drift is more pronounced when the effective population size is small.

Pleiotropy
The situation in which a single gene influences multiple phenotypic traits. This places more constraint on the gene and can reduce its rate of evolution.

Purifying selection
Negative selection against deleterious mutations. This is thought to be the most prevalent form of natural selection.

Retroduplication
A mechanism that creates duplicate gene copies in new genomic positions through the reverse transcription of mRNAs from source genes (also known as retroposition).

Sexual antagonism
Conflict arising from traits that are beneficial to one sex but harmful to the other.

Slightly deleterious mutations
Mutations with a very small negative effect on fitness. When effective population size is low, their probability of fixation is mainly governed by stochastic events.

Standing variation
Existing genetic variation that is the result of past mutations that have become neither lost nor fixed in a population.

Trans-regulatory changes
Sequence changes that alter the expression of genes located on different chromosomes or far away on the same chromosome.

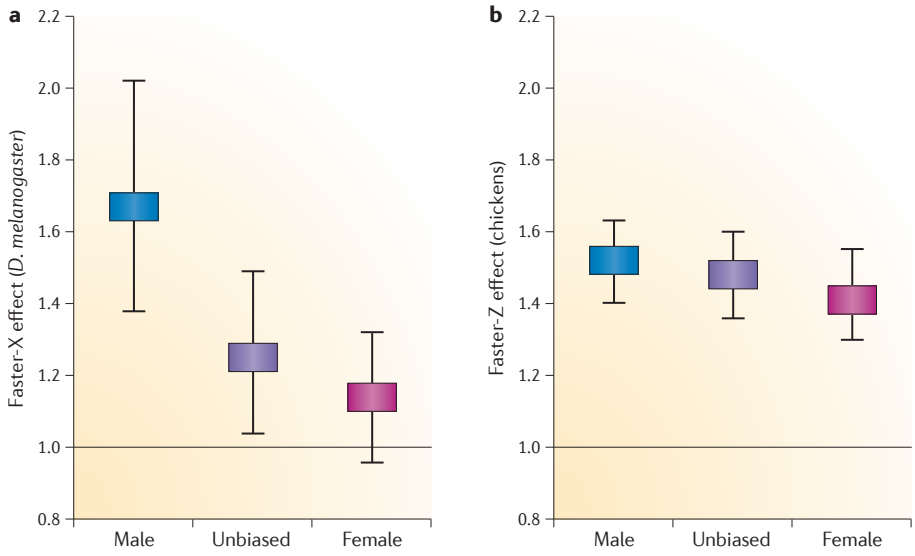

Figure 3 | **Sex-biased expression and the 'faster-X' effect.** Shown are the X/autosome ratios of protein evolution as determined by the relative rates of nonsynonymous and synonymous substitution (d_N / d_S) for each class of gene (that is, male-biased, female-biased and unbiased). The box indicates the mean, and the error bars represent the 95% confidence interval as determined by 1,000 bootstrap replicates. **a** | Data from *Drosophila melanogaster*[53], an XY species in which male-biased genes show the greatest faster-X effect. **b** | Data from chickens[49], a ZW species that shows a strong faster-Z effect but no difference among the sex-biased expression classes.

depends on several other factors, including the overall N_e, the relative N_e values of the X chromosome and autosomes, and whether adaptation occurs from new mutations or from standing variation[42,43]. For example, species with an overall small population size and/or a smaller N_e of the X chromosome than of the autosomes could show a faster-X effect owing to an increased fixation rate of slightly deleterious mutations on the X chromosome[43].

The analysis of sex-biased genes can help to elucidate the causes of faster-X evolution in different species. In male heterogametic species, male-biased genes are expected to show the greatest faster-X effect caused by the fixation of beneficial mutations, as mutations in these genes should primarily exert their effects in males, where the X chromosome is hemizygous. By contrast, female-biased genes are expected to show less of a faster-X effect, as mutations in these genes should mainly exert their effects in females, which always have two copies of the X chromosome. The above situation would be reversed in ZW taxa: female-biased genes would be expected to show the greatest faster-Z effect, and male-biased genes would be expected to exhibit the least effect. An analysis of sex-biased gene evolution in *Drosophila* spp. confirmed that male-biased genes show the greatest faster-X effect[44] (FIG. 3a), which is consistent with there being a high rate of adaptive evolution in *Drosophila* spp.[45], especially for male-biased genes[44]. In this case, the predominance of adaptive substitutions between *Drosophila* spp. allows the signal of beneficial changes to be distinguished from the background noise caused by neutral or slightly deleterious changes[46,47]. By contrast, although chickens show a strong faster-Z effect across all genes[48], the effect is no greater for female-biased genes than it is for male-biased genes[49] (FIG. 3b). This suggests that the faster-Z evolution is not driven by the fixation of recessive beneficial mutations but is instead driven by the fixation of slightly deleterious mutations that occurs due to genetic drift. The difference between *Drosophila* spp. and chickens may be explained by differences in N_e (which is much greater in *Drosophila* spp. than in chickens) and in the ratio of N_e of the X (or Z) chromosome to the autosomes (which is almost 1 in ancestral *Drosophila* populations but much less than 1 in chickens)[50]. Moreover, the absence of global dosage compensation in chickens potentially makes the interpretation of sex-biased expression of sex-linked genes different compared to taxa in which such compensation occurs.

A faster-X effect for gene expression divergence has recently been reported for several *Drosophila* species[51,52]. Like the above results for protein sequence evolution, the effect is strongest for male-biased genes, suggesting that the positive selection of recessive mutations is responsible. If so, this implies that most adaptive changes in gene expression occur within *cis*-regulatory elements and that their effects on gene expression are non-additive[52].

Conclusions

Recent studies have shown that, in addition to gene-specific processes such as regulatory element evolution and gene duplication, chromosome-wide processes such as dosage compensation have an important role in shaping sex-biased gene expression. It is now clear that global sex-chromosome dosage compensation is absent in many species and perhaps even in all ZW taxa. The systematic application of RNA-seq technologies will help to delineate the taxonomic range and mechanistic nature of dosage compensation in the near future. In terms of molecular evolution, the expansion of transcriptomic studies to multiple tissue types and developmental stages will provide a more nuanced picture of sex-biased gene expression and will help to disentangle the many factors that influence evolutionary rate. These include gene-specific factors, such as sex-biased expression and expression breadth, as well as population-level parameters, such as N_e and the relative N_e values of the X chromosome and the autosomes. The interplay of these factors can result in differences in the evolution of sex-biased genes between taxa. Conversely, similarities in sex-biased gene evolution observed between taxa may result from the action of different evolutionary forces. A major challenge for the future is to determine how variation in sex-biased gene expression affects the morphology, physiology and behaviour of males and females and how, in turn, these phenotypes affect fitness in the two sexes. An important step will be to determine the extent to which differences between the sexes in transcript levels reflect differences in their corresponding protein levels. As with most biological phenomena, the complexity of sex-biased gene expression appears to increase as more research is carried out. It is almost certain that new and unexpected discoveries lie just around the corner.

John Parsch is at the Department of Biology II, University of Munich (LMU), Grosshaderner Strasse 2, 82152 Planegg–Martinsried, Germany.

Hans Ellegren is at the Department of Evolutionary Biology, Uppsala University, Norbyvägen 18D, SE-752 36 Uppsala, Sweden.

e-mails: parsch@bio.lmu.de; Hans.Ellegren@ebc.uu.se

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Competing interests statement

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FURTHER INFORMATION

John Parsch's homepage: http://evol.bio.lmu.de/research/john_parsch

Hans Ellegren's homepage: http://www.ebc.uu.se/Research/IEG/evbiol/research/Ellegren

ALL LINKS ARE ACTIVE IN THE ONLINE PDF