Synthesis

Sex Chromosomes and the Evolution of Sexual Dimorphism: Lessons from the Genome

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ABSTRACT: Females and males of many animals exhibit a striking array of sexual dimorphisms, ranging from the primary differences of the gametes and gonads to the somatic differences often seen in behavior, morphology, and physiology. These differences raise many questions regarding how such divergent phenotypes can arise from a genome that is largely shared between the sexes. Recent progress in genomics has revealed some of the actual genetic mechanisms that create separate sex-specific phenotypes, and the evidence indicates that thousands of genes across all portions of the genome contribute to male and female forms through sex-biased gene expression. Related work has begun to define the strength and influence of sex-specific evolutionary forces that shape these phenotypic dimorphisms and how they in turn affect the genome. Additionally, theory has long suggested that the evolution of sexual dimorphism is facilitated by sex chromosomes, as these are the only portions of the genome that differ between males and females. Genomic analysis indicates that there is indeed a relationship between sexual dimorphism and the sex chromosomes. However, the connection is far more complicated than current theory allows, and this may ultimately require a reexamination of the assumptions so that predictions match the accumulating empirical data.

Keywords: sexual antagonism, sex-biased gene expression, evolutionary genomics, X chromosome, Z chromosome.

Sexual reproduction in itself does not require any real sexual dimorphisms, simply the fusion of two haploid gametes. Initially isogamous, with gametes of similar size and function, this process usually follows an evolutionary progression to anisogamy, resulting in recognizably different sperm and ova (Parker et al. 1972). Anisogamy requires some specialization of the gonad to produce and perhaps deliver the different gametic forms, but the evolution of anisogamy itself does not necessarily entail any further sexual dimorphism. Many organisms exist in this state, with sex-specific gonads and gametes encapsulated in a largely identical soma.

So, then, why are there so many organisms with distinct secondary sexual characteristics, which for the purposes of this review we will take to mean sex-specific features of the soma? Somatic dimorphisms in metazoans may take many forms, including coloration, size, shape, and behavior. Some of these somatic dimorphisms evolve to aid in actual reproduction, in either the production or the care of offspring. For example, many species of fish show clear parental care dimorphisms, with males rather than females in many species guarding, cleaning, and otherwise tending to the developing young (Mank et al. 2005). These types of behavioral dimorphisms clearly aid in the production and care of offspring and represent the necessary adaptations that accompany more complex reproductive strategies.

Yet this is far from the end of the story. Many organisms take this a step further, evolving complex, often ostentatious sexual dimorphisms that seem to play no role in the actual production or care of progeny. Rather, they are the result of either inter- or intrasexual mating competition, and many of these sexual dimorphisms have important functions in reproductive behavior and mate choice and are therefore subject to powerful sexual selection pressures (Andersson 1994).

The prevalence and degree of sexual dimorphism in the metazoans beg several questions. How do these sex-specific phenotypes arise from a genome that is largely identical in females and males? Additionally, given that the sex chromosomes are the only portion of the genome that, where they exist at all, differs between the sexes, what is the relative role of the sex chromosomes in fostering the evolution and development of sexual dimorphism? Finally, what are the evolutionary forces necessary to shape sexual dimorphisms, and how do these forces affect the genome?

There is a complex body of evolutionary theory (e.g., Rice 1984; Kirkpatrick and Hall 2004; Albert and Otto 2005) that predicts the answers to some of these questions.

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At the same time, progress in evolutionary genomics and transcriptomics has made possible the robust testing of many of these hypotheses. For instance, global transcription profiling in a range of animals has indicated that thousands of genes distributed throughout the genome contribute to sexual dimorphisms of both the gonad and the soma (Parisi et al. 2004; Yang et al. 2006; Mank et al. 2008*b*; Reinius et al. 2008). Comparative genomics has also begun to indicate the strength and molecular signal of sex-specific evolutionary forces (Meiklejohn et al. 2003; Ranz et al. 2003; Counterman et al. 2004; Zhang et al. 2004; Connallon 2007; Mank et al. 2007*a*, 2007*b*; Baines et al. 2008). However, despite the obvious potential synergies, progress in evolutionary theory and comparative genomics has proceeded, to a surprising degree, independently. This was in the past at least partly due to the expense and technical difficulties associated with genomic analysis; however, postgenomic advances in whole-genome sequencing and expression analysis make such an excuse untenable today.

In this synthesis, I will attempt to integrate how we think sexual dimorphisms should evolve with genomic data that show how they actually do evolve. Additionally, I will discuss how sex-specific evolutionary pressures, which shape sexual dimorphisms, affect the genome and, ultimately, the phenotype.

The Genomic Landscape of Sexually Dimorphic Phenotypes

Sexually dimorphic phenotypes are fashioned by those selective pressures that differ between the sexes and indicate where the reproductive fitness interests of males and females diverge (Chippindale et al. 2001). When sex-specific evolutionary forces act opposite each other, the resulting antagonism produces a phenotype that represents the fulcrum balancing female- and male-specific selective pressures but that is generally optimal for neither sex alone. This antagonism is resolved when some mechanism acts to decouple the male and female phenotype, achieving sex-specific fitness optima. This process has occurred countless independent times in metazoan evolution and has produced some truly bizarre adaptations (see Judson 2002). Though the process and the dimorphisms themselves are convergent, the underlying mechanism is often conserved, as many dimorphisms are controlled ultimately by steroid sex hormones (Zauner et al. 2003; Ketterson et al. 2005; Mank 2007*a*) that control the genes underlying sex-specific phenotypes via androgen- or estrogen-binding regulatory factors (Reinius et al. 2008).

The Role of Sex Chromosomes

Most sexual dimorphisms are, to some degree, heritable, hinting at an ultimate genetic mechanism. Because these phenotypes are by definition sex biased or sex limited, there is an immediately logical association with the sex chromosomes, which are also sex biased or sex limited in transmission and distribution. A rich and complex body of theory developed describing why sexual dimorphisms would be more often sex linked (from Rice 1984), which, for the purposes of this review, I intend to mean harbored on a sex chromosome. Additionally, sex chromosomes can take either of two inheritance patterns: female heterogamety, observed in birds and Lepidoptera, results in a ZW karyotype in females and a ZZ karyotype in males, while male heterogamety, seen in mammals and *Drosophila*, produces XX females and XY males. Theory developed to describe how sexual dimorphism, particularly that due to sexual selection, would evolve in clades with the different sex chromosome types (Reeve and Pfennig 2003; Kirkpatrick and Hall 2004; Albert and Otto 2005), since female- and male-heterogametic sex chromosomes have converse sex bias in inheritance and therefore sex-specific selection pressures (for a schematic of sex chromosome types and related selection pressures, see fig. 1).

Much of this theory is based on sexual antagonism, where a single locus benefits one sex at the expense of the other. In single-locus antagonism models, there is a predicted association between antagonistic loci and the sex chromosome (Rice 1984), as these are the only portions of the genomes that, due to the fact that they are disproportionately distributed between males and females, experience sex-biased selection on a chromosomal scale. Sexual selection theory developed on this model, with the assumption that sexually selected phenotypes were controlled by one or just a few loci and that they were sexually antagonistic.

What these theories gave the discipline was something that, as scientists, we crave: a testable hypothesis. This hypothesis then framed the corresponding empirical research in a subtle but important way. The question was not so much about the mechanisms by which sexually dimorphic traits evolve. Rather, the theory directed empirical studies to ask whether sex chromosomes were a hot spot (having an effect disproportionate to their size) regardless of what the actual proportion was relative to the genome as a whole. These foci are quite different and have the power to shape experimental design, interpretation, and even publication a great deal.

Considerable effort has been put to explicitly testing how these traits relate to the sex chromosomes using whole phenotypes, with results that are less than ironclad. Anecdotal species-specific reports (Iyengar et al. 2002; Saether

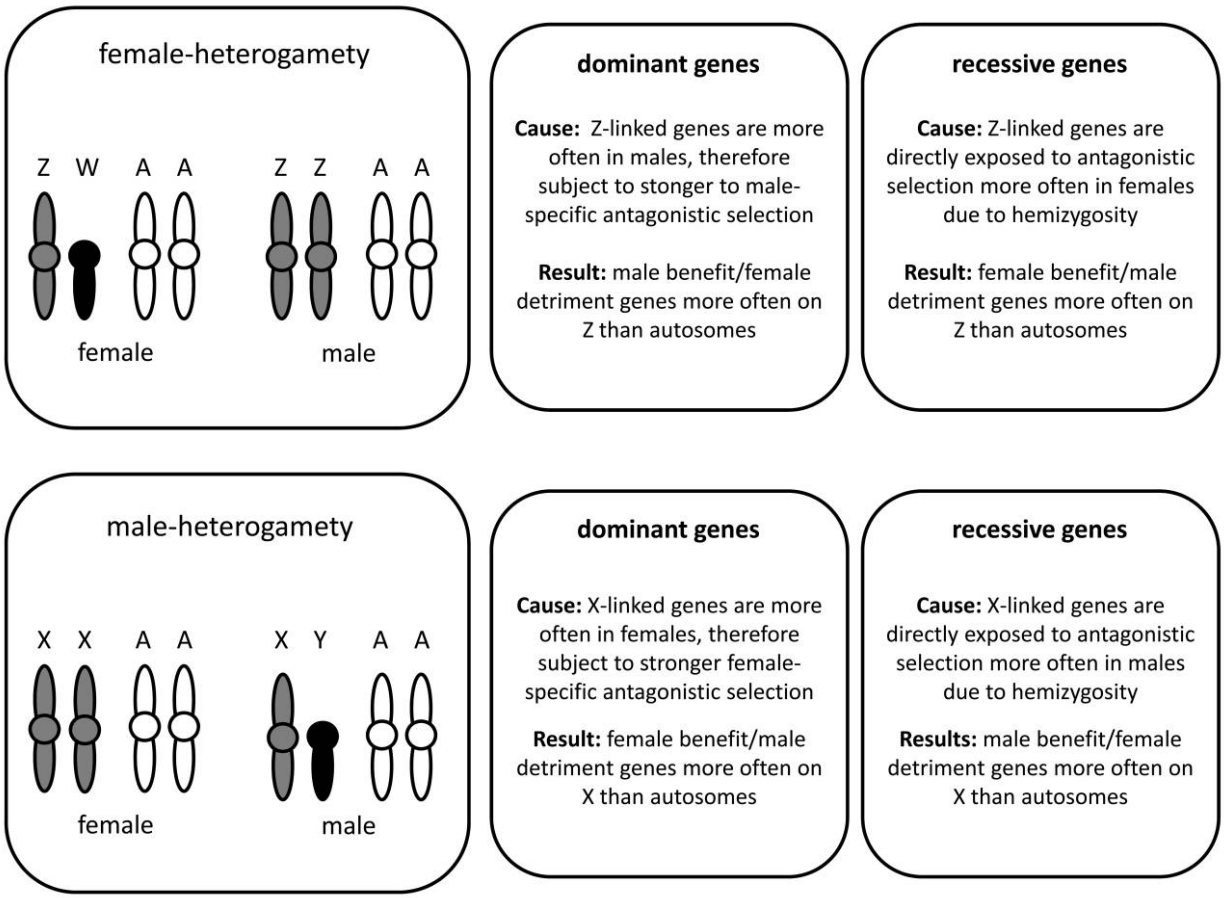

Figure 1: Expected genomic distribution of sexually antagonistic single loci, according to predictions developed by Rice (1984). For both male- and female-heterogametic systems, the major sex chromosome is shown in gray, the sex-limited minor chromosome in black, and the autosomes in white.

et al. 2007) and limited surveys (Reinhold 1998; Lindholm and Breden 2002; Reeve and Pfennig 2003) provided supporting evidence. However, many species-specific surveys do not indicate a disproportionately large role for the sex chromosomes (Ritchie 2000; Wolfenbarger and Wilkinson 2001).

Given that there are exceptions to nearly every evolutionary theory, it is difficult to interpret anecdotal data as they relate to the hypothesized link between sex chromosomes and sexual dimorphisms. Broad and comprehensive surveys are fairer tests, as they average the evidence to derive a consensus, and such studies have not conformed to theoretical predictions. A complete genome scan of *Drosophila* sexually selected quantitative trait loci indicated no excess contribution of the X chromosome (Fitzpatrick 2004). Additionally, the only broadscale phylogenetically controlled test of the theory at the phenotypic level did not support the association between sex chromosome type and sexually selected traits (Mank et al. 2006*b*), and an extensive survey of the literature indicates that the evidence is profoundly mixed (Fairbairn and Roff 2006 and references therein).

This does not by any means suggest that sex chromosomes do not play an important role in the evolution of sexually dimorphic phenotypes. At the most basic level, sex chromosomes, where they exist, harbor the ultimate sex-determining mechanisms and so initiate gonadal differentiation. However, while sex-determining genes may induce downstream genes underlying somatic sexual dimorphism, as is seen in male-specific pigmentation in *Drosophila melanogaster* (Kopp et al. 2000), the actual genes that control sex determination and sexual differentiation of the gonad and those underlying somatic sexually dimorphic traits are largely nonoverlapping (Mank et al. 2008*b*), and it is important to make this distinction in testing the theory linking sexually dimorphic traits to the

Table 1: Relative contribution of the X and Z chromosomes to the assembled genomes of several metazoans

Species	No. X or Z protein coding genes[a]	Percent of total protein coding genes	Size of X or Z (Mb)	Percent of genome[b]
Vertebrates:				
Zebrafish	0	0	0	0
Chicken	734	4.4	74.6	7.1
Opossum	448	2.3	79.3	2.3
Dog	766	4.0	126.9	5.3
Mouse	993	4.2	166.7	4.9
Human	920	4.1	154.9	5.0
Invertebrates:				
Anopheles	1,088	8.7	24.4	8.8
Drosophila	2,224	15.7	22.4	13.3
C. elegans	2,801	13.9	17.7	17.7

[a] Known, projected, and novel protein coding genes from July 2008 Ensembl annotation (http://www.ensembl.org)

[b] Total base pairs in July 2008 Ensembl build.

sex chromosomes. A number of positive associations between sex chromosomes and sexually dimorphic phenotypes indicate that there is indeed some connection beyond initial sex determination. However, the lack of a consistent signal across all metazoans suggests that the nature of sexually dimorphic phenotypes is far more complex than current models take into account.

The Role of Autosomes

There is a quietly growing body of evidence that some sexually selected traits are not as simple as first assumed, and this newly realized complexity may limit the role of sex chromosomes in the evolution of female and male phenotypes. First, sexually selected traits may not be sexually antagonistic at all at inception. It was assumed that because sexually selected traits were sexually dimorphic, they benefited one sex (presumably males in traditional thinking) and were detrimental to the other. By this reasoning, the traits would have initially been expressed in both sexes, and sexually antagonistic selection would then act to confine it only to the sex that benefits. Evidence from bird hybrids suggests that there may be no initial underlying antagonism or rather that the traits are sex limited at the outset (Coyne et al. 2008), and this could arise for those genes that are controlled by hormone-binding promoter elements. Sexually selected traits are often regulated by androgen receptors (Enstrom et al. 1997; Hill et al. 1999; Zauner et al. 2003; Mank 2007*a*), and if emerging sexual selection pressures act on genes with preexisting androgen promoters, the resulting trait would be sex limited at the outset and therefore would not be subject to sexually antagonistic selection in the opposite, nondisplaying sex. However, this scenario would gradually change, as directional selection for increased testosterone in males produced a correlated and antagonistic increase in females (Clotfelter et al. 2004; Ketterson et al. 2005; Mank 2007*a*).

Other realities of sexually selected traits create further problems with theoretical models. We now know that many sexually selected traits are highly variable, implying polygenic underpinnings (Gleason et al. 2002; Chenoweth et al. 2008; Poissant et al. 2008). Polygenic traits are far more difficult to model, and it is not yet known how this would affect sex linkage under a range of scenarios. Additionally, the genes underlying sexually selected traits have other functions (Fitzpatrick 2004; Ducrest et al. 2008), and this pleiotropy can hinder the evolution of sexual dimorphism (Mank et al. 2008*a*). While metazoan systems biology is still in its infancy, the initial studies of genetic and biochemical networks and pathways indicate that the assumptions of simplicity and additivity necessary to make these models work may be unfair for a sizable proportion of genes underlying dimorphic phenotypes.

All this suggests that the autosomes are doing some amount of the heavy lifting regarding the evolution of sexual dimorphism. Additionally, with the exception of some invertebrates such as *Drosophila*, the sex chromosomes comprise a small fraction of the total DNA and protein-coding genes of the whole genome (table 1). Even if the contribution of sex chromosomes to the evolution of sexual dimorphism is larger than their relative physical size or genic content, in all likelihood, the role of the sex chromosomes is still far less than that of the autosomal component.

As further evidence that autosomes are a major player,

many species show clear sexual dimorphisms but lack sex chromosomes, or even constitutive sex-determining genes, entirely. For example, many sequentially hermaphroditic species of fish, which by their nature have inducible and nonchromosomal mechanisms of sex determination that are present in all individuals, are sexually dichromatic, particularly in the Labridae, Scaridae, and Gobiidae families (see Mank et al. 2006*a*; Mank 2007*b* and supplemental materials therein). That sexual dimorphisms exist in lineages entirely free of sex chromosomes indicates that genes encoding sexual-dimorphic traits may quite happily reside on the autosomes.

We should also consider the growing body of evidence regarding epigenetics and how this form of non-Mendelian inheritance affects the evolution of the phenotype. Imprinting allows for sex-specific expression of autosomal alleles, and this is another effective way to resolve sexual conflict without explicitly involving sex chromosomes (Day and Bonduriansky 2004). In mammals, there is a growing catalog of imprinted (Morison et al. 2005) or otherwise epigenetically regulated (Mikkelsen et al. 2007) genes, indicating strong potential involvement in the evolution of sexual dimorphism.

While these complexities, in combination with strong, possibly untrue, assumptions, likely limit the role of the sex chromosomes in the evolution of female and male phenotypes, little effort has been put into explicitly studying the role of the autosomes in sexually dimorphic traits because of the perceived doctrine that these traits are facilitated, even dependent on, sex chromosome linkage. Additionally, given that phenotypes are an amalgam of numerous tangled selective pressures, organismal constraints, and genomic evolvabilities, perhaps it is not so surprising that there are difficulties in extrapolating from the phenotype in testing theories about genomic distribution. These complications indicate that some dimorphic phenotypes are too complex to be accounted for with generalities.

The Genomic Landscape of Sexually Dimorphic Genes

When complexity makes it difficult to test theories, it can be useful to simplify the system. The dawning of the transcriptomic era has demonstrated that thousands of genes show patterns of sex-biased expression in many animals (Ranz et al. 2003; Yang et al. 2006; Mank et al. 2008*b*; Reinius et al. 2008), and these genes, or some subset of them, are the actual basis of the dimorphic phenotypes we observe. However, unlike phenotypes, which represent the net results of a tangle of contradictory evolutionary forces acting on an undefined number of distinct genomic targets, sex-biased genes are single loci, and this simplifies the assumptions that go into any predictive theory regarding them.

Additionally, sex-biased gene expression can be used as a proxy for single-locus sexual antagonism, where the expression level is simultaneously advantageous to one sex and disadvantageous to the other (Connallon and Knowles 2005). In cases like this, the expression pattern will be a balance between the selective pressures in both sexes but will be optimal for neither until some regulatory mechanism evolves to decouple the male and female expression levels. This allows for sex-specific expression levels and fitness optima and effectively resolves the evolutionary conflicts between males and females. Therefore, sex-biased expression can be used as a beacon of previously resolved sexual antagonism.

This is not to say that sex-biased expression is a perfect proxy, as the correlation of expression differences and sexual antagonism can be affected by evolutionary restrictions. First, it must take a certain amount of time between the origin of antagonism and the evolution of regulatory mechanisms to resolve it. While sex-biased expression can change relatively quickly across a closely related clade for some genes (Zhang et al. 2007; Reinius et al. 2008), it remains a complex expression pattern, and therefore the evolution of the required regulatory machinery cannot be trivial. This suggests that nascent antagonism may still reside unresolved in the genome. Second, the initial studies of sex bias from a systems biology perspective indicate that certain conditions, namely, pleiotropic constraint, may hinder the evolution of sex bias and therefore leave a certain subset of pleiotropic genes with unresolved antagonism (Mank et al. 2008*a*). Pleiotropic genes by definition have many, often unrelated functions, and it is likely that some of the functions of pleiotropic genes cannot tolerate sex-biased expression resulting from sexual antagonism in other functionalities. These studies suggest that using sex-biased expression as an indicator of sexual antagonism misses newly emergent and multifunctional antagonistic genes.

That said, sex bias is at this point the only indicator of sexual antagonism that we can apply at the level of the genome. Additionally, there is no reason to think that these biases would affect some genomic regions more than others. Given that assumption, it is possible to use these genes to test the theories regarding their distribution, and results from several studies indicate that sex-biased genes show distinct, nonrandom genomic distributions. If one accepts the further assumption that female bias indicates a gene with simultaneous female benefit and male detriment and male bias similarly indicates male benefit and female detriment, these distributions are startlingly consistent with predictive theory regarding single-locus sexual antagonism (Rice 1984). Evidence from male-heterogametic systems is

convergent: the X chromosome is depauperate in male-biased genes in *Drosophila* (Parisi et al. 2003; Ranz et al. 2003; Sturgill et al. 2007) and mammals (Khil et al. 2004). Evidence from female-heterogametic systems is limited to birds, but they show a clear overrepresentation of Z-linked male-biased genes than would be assumed from chance alone (Kaiser and Ellegren 2006; Storchova and Divina 2006).

This seemingly incontrovertible proof would suggest that the subject was resolved; however, we cannot close the case just yet. Genomes are, for lack of a better word, quirky. This is reasonable when you consider how such a relatively limited subset of genes (15,000–20,000 for most metazoans), many of which, remarkably, are conserved over hundreds of millions of years, gives rise to such an extraordinary diversity of forms. Additionally, because evolution is an incremental and historical process that acts by bending past adaptations to new functions, the genome is something of a Rube Goldberg machine, often performing simple tasks in a convoluted and circuitous way (surely no intelligent architect would claim to have designed the full genetic network map of any eukaryote, with all its myriad redundancies, circularities, and meandering signaling pathways). This is relevant to the question at hand because recent experiments have shown that nonrandom distribution of sex-biased genes seen in *Drosophila*, mammals, and birds are, in fact, due to regulatory idiosyncrasies of chromosome inactivation and dosage rather than sexually antagonistic selection.

The paucity of male-biased genes on the *Drosophila* X is primarily explained by the fact that the X chromosome is transcriptionally silenced during postmeiotic spermatogenesis (Hense et al. 2007). Regardless of whether the whole or simply a majority of the X is inactivated, the greater part of sex-linked genes that function in late spermatogenesis must be either prestocked before silencing or located on the autosomes. Though a handful of genes are known to escape (Namekawa et al. 2006), similar silencing exists in mammals (Turner 2007), and this accounts for both the overabundance of female-biased genes on the X and the out-of-X migration that can be used to date the origin of sex chromosome silencing (Potrzebowski et al. 2008). Fair tests of nonrandom genomic distribution for sex-biased genes in mammals and flies must account for these regulatory patterns, and initial tests bear out the theory, at least in mice. When meiotic silencing is accounted for, the murine X chromosome shows an overrepresentation of male-biased genes expressed in the gonad (Mueller et al. 2008). Further testing may be best accomplished with somatic tissue, where the disadvantages from fewer overall sex-biased genes are balanced by the continuous transcription from the sex chromosomes.

Birds also have genomic regulatory quirks, though of an entirely different flavor. Contrary to mammals (Lyon 1999; Nguyen and Disteche 2006; Lin et al. 2007; Johnston et al. 2008), *Drosophila* (Lucchesi et al. 2005; Gupta et al. 2006), and *C. elegans* (Meyer and Casson 1986; Meyer et al. 2004), birds have no wholesale mechanisms to balance out the dosage effects of the sex chromosomes (Ellegren et al. 2007; Itoh et al. 2007). At this point we do not know whether the lack of dosage compensation is limited to birds or whether it is characteristic of female heterogamety in general, but the implication regardless is that dosage compensation is not a necessary product of sex chromosome evolution. This in turn leads to questions about how such complicated genomic mechanisms occur if they are not required and what actual evolutionary and regulatory roles they fill. At any rate, the lack of dosage compensation on the Z means that by default of dosage effects, rather than regulatory resolution of sexual antagonism, Z-linked genes are male biased.

As with male-heterogametic animals, fair assessment of the association of sex-biased genes and the Z require that these peculiarities, in this case the lack of dosage compensation, be accounted for. Preliminary dosage-free tests based on changes in sex-biased expression between embryonic and adult time points (Mank and Ellegren, forthcoming) indicate that there is an excess of male-benefit genes on the Z equivalent to roughly double what would be expected based on the chromosome's relative size.

Global transcription profiling of sex-biased gene expression has also revealed that, regardless of the role of the sex chromosomes relative to their size, the autosomes harbor the lion's share of sex-biased genes in mice (Yang et al. 2006), birds (Mank et al. 2008*b*), and flies (Parisi et al. 2004). However, transcription profiling methods compress the multidimensional pathway and network structure of gene expression into a one-dimensional snapshot of transcriptional activity, and we do not yet know whether sex-biased autosomal genes hold apical positions in signaling pathways or whether autosomal sex-biased gene expression is simply a downstream effect of induction by sex-biased genes on the sex chromosomes.

Evolution of Sexual Genomes

The explosion of sequence and transcriptional data on a variety of animals makes it possible to begin parsing out the female- and male-specific evolutionary pressures that shape sexual dimorphisms and to begin determining their effect on the genome. The emerging consensus suggests that sex-specific evolutionary pressures are significant and have a profound effect on the evolutionary trajectory of the genes underlying sexually dimorphic phenotypes. This initially may not be surprising, given molecular evolutionary studies comparing sex-linked genes with autoso-

mal genes (reviewed in Vicoso and Charlesworth 2006 for male-heterogametic systems and in Mank et al. 2007*a* for female-heterogametic systems). However, the accelerated rates of evolution observed in sex-linked genes are due to hemizygosity of the heterogametic sex. Therefore, these patterns do not represent sex-specific selection so much as either different selective exposure in males and females or different levels of genetic drift among the chromosomal classes (Charlesworth et al. 1987).

Sex-biased genes are the product of different male- and female-specific evolutionary pressures and therefore can be used to measure sex-specific selection with molecular sequence data. If we follow this line of argument, female-biased genes are under stronger female-specific selection pressures, and the converse is true for male-biased genes. In most species where sexual selection pressures act more forcefully on male phenotypes (Andersson 1994), the logical expectation is that the male-biased genes that underlie these phenotypes respond to this increased selective pressure with accelerated rates of protein evolution.

As with genomic distribution of sex-biased genes, initial results fit beautifully with predictive theory. In a variety of metazoans, male-biased genes in the adult gonad (or, in the case of small metazoans, from whole animals where the stronger sex-biased expression levels of the gonad drown out the majority of the signal from the soma) show elevated rates of protein evolution (Zhang et al. 2004; Cutter and Ward 2005; Good and Nachman 2005; Khaitovich et al. 2005; Pröschel et al. 2005; Turner et al. 2008). Male-biased genes in the gonad are putatively associated with spermatogenesis; therefore, the accelerated rate of evolution for this class of genes is in line with what would be expected from positive selection from sperm competition.

Sexual selection also acts on sex-specific behaviors, which in turn theoretically arise from sex-biased gene expression patterns in the brain. Female choice for male behaviors would theoretically exert strong selective pressure on the male-biased genes underlying them, and so it is logical that male-biased neurological genes would show the same patterns as gametogenic coding regions. Primates conform to this model, and even more interestingly, the amount of sex-biased expression in primates seems to correlate with the degree of sexual dimorphisms exhibited by the species (Reinius et al. 2008).

Birds, however, show the opposite pattern of divergence, with accelerated rates of evolution for female-biased but not male-biased brain genes (Mank et al. 2007*b*), which is difficult to explain with sexual selection theory, as many bird species exhibit male behavioral phenotypes that are key to species recognition and female mate choice. There are two alternative rationalizations for the strange pattern seen in avian neurological tissue. First, the only study to date in birds is unusual in that it derives from late embryonic samples, and it may be that sex-biased selection changes over the course of the lifetime. If true, this suggests that ontogeny interacts with sex-specific evolutionary pressures and that the molecular beacon of these pressures shifts over the course of the life cycle. Alternatively, rapid rates of evolution can be explained by either strong positive selection or relaxed constraints. It is possible that, for some reason I have yet to fathom, female brains are subject to less purifying selection than male brains.

Regardless of conflicting evolutionary signatures observed on sex-biased genes, the implication from all of these studies is that the presence of sexual dimorphism can profoundly influence the evolution of the genome. This means that the evolution of sex-specific phenotypes is a circular process, with sex-specific selective forces shaping the expression of the underlying genes to produce dimorphic phenotypes that in turn affect the evolutionary signature of the DNA molecule itself.

Conclusions

Sexual selection and sexual dimorphism have captivated evolutionary biologists since Darwin, and this fascination has led to a rich body of theory and countless empirical phenotypic studies. Now, the availability of ever-increasing genome-sequencing and transcriptome-profiling capabilities have made it feasible to answer traditional evolutionary questions about the evolution of sexual dimorphism with fine-scale precision in a wide array of animals and to parse female- and male-specific selection pressures from the tangle of evolutionary forces shaping the phenotype.

While these new approaches have made progress, further integration of genomic and organismal evolutionary approaches is needed to address several outstanding questions regarding the evolution of sexual dimorphism. First, how are sex-biased genes linked to sexually dimorphic phenotypes in a functional context? Additionally, how does mating system, which bears a clear relationship with the evolution of dimorphic phenotypes, shape related gene expression and molecular sequence patterns? Finally, what are the functional and organismal constraints on gene expression, and how do these affect the evolution of sexually dimorphic phenotypes? The answers to these types of questions, which could previously only be guessed at, are now possible to address with dovetail genomic and evolutionary tactics.

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Literature Cited

Albert, A. Y. K., and S. P. Otto. 2005. Sexual selection can resolve sex-linked sexual antagonism. Science 310:119–121.

Andersson, M. 1994. Sexual selection. Princeton University Press, Princeton, NJ.

Baines, J. F., S. A. Sawyer, D. L. Hartl, and J. Parsch. 2008. Effects of X-linkage and sex-biased gene expression on the rate of adaptive protein evolution in *Drosophila*. Molecular Biology and Evolution 25:1639–1650.

Charlesworth, B., J. A. Coyne, and N. H. Barton. 1987. The relative rates of evolution of sex chromosomes and autosomes. American Naturalist 130:113–146.

Chenoweth, S. F., H. D. Rundle, and M. W. Blows. 2008. Genetic constraints and the evolution of display trait sexual dimorphism by natural and sexual selection. American Naturalist 171:22–34.

Chippindale, A. K., J. R. Gibson, and W. R. Rice. 2001. Negative genetic correlation for adult fitness between sexes reveals ontogenetic conflict in *Drosophila*. Proceedings of the National Academy of Sciences of the USA 98:1671–1675.

Clotfelter, E. D., D. M. O'Neal, J. M. Gaudioso, J. M. Casto, I. M. Parker-Renga, E. A. Snajdr, D. L. Duffy, et al. 2004. Consequences of elevating plasma testosterone in females of a socially monogamous songbird: evidence of constraints on male evolution? Hormones and Behavior 46:171–178.

Connallon, T. 2007. Adaptive protein evolution of X-linked and autosomal genes in *Drosophila*: implications for faster-X hypotheses. Molecular Biology and Evolution 24:2566–2572.

Connallon, T., and L. L. Knowles. 2005. Intergenomic conflict revealed by patterns of sex-biased gene expression. Trends in Genetics 21:495–499.

Counterman, B. A., D. Ortiz-Barrientos, and M. A. F. Noor. 2004. Using comparative genomic data to test for fast-X evolution. Evolution 58:656–660.

Coyne, J. A., E. H. Kay, and S. Pruett-Jones. 2008. The genetic basis of sexual dimorphism in birds. Evolution 62:214–219.

Cutter, A. D., and S. Ward. 2005. Sexual and temporal dynamics of molecular evolution in *C. elegans* development. Molecular Biology and Evolution 22:178–188.

Day, T., and R. Bonduriansky. 2004. Intralocus sexual conflict can drive the evolution of genomic imprinting. Genetics 167:1537–1546.

Ducrest, A.-L., L. Keller, and A. Roulin. 2008. Pleiotropy in the melanocortin system, coloration and behavioral syndromes. Trends in Ecology & Evolution 23:502–510.

Ellegren, H., L. Hultin-Rosenberg, B. Brunström, L. Dencker, K. Kultima, and B. Scholtz. 2007. Faced with inequality: chicken does not have general dosage compensation of sex-linked genes. BMC Biology 5:40.

Enstrom, D. A., E. D. Ketterson, and V. Nolan. 1997. Testosterone and mate choice in the dark-eyed junco. Animal Behaviour 54: 1135–1146.

Fairbairn, D. J., and D. A. Roff. 2006. The quantitative genetics of sexual dimorphism: assessing the importance of sex-linkage. Heredity 97:319–328.

Fitzpatrick, M. J. 2004. Pleiotropy and the genomic location of sexually selected genes. American Naturalist 163:800–808.

Gleason, J. M., S. V. Nuzhdin, and M. G. Ritchie. 2002. Quantitative trait loci affecting a courtship signal in *Drosophila melanogaster*. Heredity 89:1–6.

Good, J. M., and M. W. Nachman. 2005. Rates of protein evolution are positively correlated with developmental timing of expression during mouse spermatogenesis. Molecular Biology and Evolution 22:1044–1052.

Gupta, V., M. Parisi, D. Sturgill, R. Nuttall, M. Doctolero, O. K. Dudko, J. D. Malley, et al. 2006. Global analysis of X-chromosome dosage compensation. Journal of Biology 5:3.

Hense, W., J. F. Baines, and J. Parsch. 2007. X chromosome inactivation during *Drosophila* spermatogenesis. PLoS Biology 5:2288–2295.

Hill, J. A., D. A. Enstrom, E. D. Ketterson, V. Nolan, and C. Ziegenfus. 1999. Mate choice based on static versus dynamic secondary sexual traits in the dark-eyed junco. Behavioral Ecology 10:91–96.

Itoh, Y., E. Melamed, X. Yang, K. Kampf, S. Wang, N. Yehya, A. van Nas, et al. 2007. Dosage compensation is less effective in birds than in mammals. Journal of Biology 6:2.

Iyengar, V. K., H. K. Reeve, and T. Eisner. 2002. Paternal inheritance of a female moth's mating preference. Nature 419:830–832.

Johnston, C. M., F. L. Lovell, D. A. Leongamornlert, B. E. Stranger, E. T. Dermitzakis, and M. T. Ross. 2008. Large-scale population study of human cell lines indicates that dosage compensation is virtually complete. PLoS Genetics 4:e9.

Judson, O. 2002. Dr. Tatiana's sex advice to all creation: the definitive guide to the evolution of sex. Metropolitan Books, New York.

Kaiser, V. B., and H. Ellegren. 2006. Nonrandom distribution of genes with sex-biased expression in the chicken genome. Evolution 60: 1945–1951.

Ketterson, E. D., V. Nolan, and M. Sandell. 2005. Testosterone in females: mediator of adaptive traits, constraint on sexual dimorphism, or both? American Naturalist 166(suppl.):S85–S98.

Khaitovich, P., I. Hellmann, W. Enard, K. Nowick, M. Leinweber, H. Franz, G. Weiss, et al. 2005. Parallel patterns of evolution in the genomes and transcriptomes of humans and chimpanzees. Science 309:1850–1854.

Khil, P. P., N. A. Smirnova, P. J. Romanienko, and R. D. Camerini-Otero. 2004. The mouse X chromosome is enriched for sex-biased genes not subject to selection by meiotic sex chromosome inactivation. Nature Genetics 36:642–646.

Kirkpatrick, M., and D. W. Hall. 2004. Sexual selection and sex linkage. Evolution 58:683–691.

Kopp, A., I. Duncan, and S. B. Carroll. 2000. Genetic control and evolution of sexually dimorphic characters in *Drosophila*. Nature 408:553–559.

Lin, H., V. Gupta, M. D. VerMilyea, F. Faliani, J. T. Lee, L. P. O'Neill, and B. M. Turner. 2007. Dosage compensation in the mouse balances up-regulation and silencing of X-linked genes. PLoS Biology 5:e326.

Lindholm, A., and F. Breden. 2002. Sex chromosomes and sexual selection in poeciliid fishes. American Naturalist 160(suppl.):S214–S224.

Lucchesi, J. C., W. G. Kelly, and B. Parming. 2005. Chromatin remodeling in dosage compensation. Annual Review of Genetics 39: 615–651.

Lyon, M. F. 1999. X-chromosome inactivation. Current Biology 9: R235–R237.

Mank, J. E. 2007*a*. The evolution of sexually selected traits and an-

tagonistic androgen expression in actinopterygiian fishes. American Naturalist 169:142–149.

———. 2007*b*. Mating preferences, sexual selection, and patterns of cladogenesis in ray-finned fishes. Journal of Evolutionary Biology 20:597–602.

Mank, J. E., and H. Ellegren. Forthcoming. Sex linkage of sexually antagonistic genes is predicted by female, but not male, effects in birds. Nature.

Mank, J. E., D. E. L. Promislow, and J. C. Avise. 2005. Phylogenetic perspectives on the evolution of parental care in ray-finned fishes. Evolution 59:1570–1578.

———. 2006*a*. Evolution of alternative sex determining mechanisms in teleost fishes. Biological Journal of the Linnean Society 87:83–93.

Mank, J. E., D. W. Hall, M. Kirkpatrick, and J. C. Avise. 2006*b*. Sex chromosomes and male ornaments: a comparative evaluation in ray-finned fishes. Proceedings of the Royal Society B: Biological Sciences 273:233–236.

Mank, J. E., E. Axelsson, and H. Ellegren. 2007*a*. Fast-X on the Z: rapid evolution of sex-linked genes in birds. Genome Research 17: 618–624.

Mank, J. E., L. Hultin-Rosenberg, E. Axelsson, and H. Ellegren. 2007*b*. Rapid evolution of female-biased, but not male-biased, genes expressed in avian brain. Molecular Biology and Evolution 24:2698–2706.

Mank, J. E., L. Hultin-Rosenberg, M. Zwahlen, and H. Ellegren. 2008*a*. Pleiotropic constraint hampers the resolution of sexual antagonism in vertebrate gene expression. American Naturalist 171: 35–43.

Mank, J. E., L. Hultin-Rosenberg, M. T. Webster, and H. Ellegren. 2008*b*. The unique genomic properties of sex-biased genes: insights from avian microarray data. BMC Genomics 9:148.

Meiklejohn, C. D., J. Parsch, J. M. Ranz, and D. L. Hartl. 2003. Rapid evolution of male-biased gene expression in *Drosophila*. Proceedings of the National Academy of Sciences of the USA 100:9894–9899.

Meyer, B. J., and L. P. Casson. 1986. *Caenorhabditis elegans* compensates for the difference in X-chromosome dosage between the sexes by regulating transcript levels. Cell 47:871–881.

Meyer, B. J., P. McDonel, G. Csankovszki, and E. Ralston. 2004. Sex and X-chromosome-wide repression in *Caenorhabditis elegans*. Cold Spring Harbor Symposia on Quantitative Biology 69:71–79.

Mikkelsen, T. S., M. C. Ku, D. B. Jaffe, B. Issac, E. Lieberman, G. Giannoukos, P. Alvarez, et al. 2007. Genome-wide maps of chromatin state in pluripotent and lineage-committed cells. Nature 448:553–560.

Morison, I. M., J. P. Ramsay, and H. G. Spencer. 2005. A census of mammalian imprinting. Trends in Genetics 21:457–465.

Mueller, J. L., S. K. Mahadevaiah, P. J. Park, P. R. Warburton, D. C. Page, and J. M. A. Turner. 2008. The mouse X chromosome is enriched for multicopy testis genes showing postmeiotic expression. Nature Genetics 40:794–799.

Namekawa, S. H., P. J. Park, L. F. Zhang, J. E. Shima, J. R. McCarrey, M. D. Griswold, and J. T. Lee. 2006. Postmeiotic sex chromatin in the male germline of mice. Current Biology 16:660–667.

Nguyen, D. K., and C. M. Disteche. 2006. Dosage compensation of the active X chromosome in mammals. Nature Genetics 38:47–53.

Parisi, M., R. Nuttall, D. Naiman, G. Bouffard, J. Malley, J. Andrews, S. Eastman, et al. 2003. Paucity of genes on the *Drosophila* X chromosome showing male-biased expression. Science 299:697–700.

Parisi, M., R. Nuttall, P. Edwards, J. Minor, D. Naiman, J. N. Lu, M. Doctolero, et al. 2004. A survey of ovary-, testis-, and soma-biased gene expression in *Drosophila melanogaster* adults. Genome Biology 5:R40.

Parker, G. A., R. R. Baker, and V. G. F. Smith. 1972. The origin and evolution of gamete dimorphism and the male-female phenomenon. Journal of Theoretical Biology 36:529–553.

Poissant, J., A. J. Wilson, M. Festa-Bianchet, J. T. Hogg, and D. W. Coltman. 2008. Quantitative genetics and sex-specific selection on sexually dimorphic traits in bighorn sheep. Proceedings of the Royal Society B: Biological Sciences 275:623–628.

Potrzebowski, L., N. Vinckenbosch, A. C. Marques, F. Chalmel, B. Jegou, and H. Kaessmann. 2008. Chromosomal gene movements reflect the recent origin and biology of the therian sex chromosomes. PLoS Biology 6:e80.

Pröschel, M., Z. Zhang, and J. Parsch. 2005. Widespread adaptive evolution of *Drosophila* genes with sex-biased expression. Genetics 174:893–900.

Ranz, J. M., C. I. Castillo-Davis, C. D. Meiklejohn, and D. L. Hartl. 2003. Sex-dependent gene expression and evolution of the *Drosophila* transcriptome. Science 300:1742–1745.

Reeve, H. K., and D. W. Pfennig. 2003. Genetic biases for showy males: are some genetic systems especially conducive to sexual selection? Proceedings of the National Academy of Sciences of the USA 100:1089–1094.

Reinhold, K. 1998. Sex linkage among genes controlling sexually selected traits. Behavioral Ecology and Sociobiology 44:1–7.

Reinius, B., P. Saetre, J. A. Leonard, R. Blekhman, R. Merino-Martinez, Y. Gilad, and E. Jazin. 2008. An evolutionarily conserved sexual signature in the primate brain. PLoS Genetics 4:e1000100.

Rice, W. R. 1984. Sex chromosomes and the evolution of sexual dimorphism. Evolution 38:735–742.

Ritchie, M. G. 2000. The inheritance of female preference functions in a mate recognition system. Proceedings of the Royal Society B: Biological Sciences 267:327–332.

Saether, S. A., G. P. Saetre, T. Borge, C. Wiley, N. Svedin, G. Andersson, T. Veen, et al. 2007. Sex chromosome-linked species recognition and evolution of reproductive isolation in flycatchers. Science 318:95–97.

Storchova, R., and P. Divina. 2006. Nonrandom representation of sex-biased genes on chicken Z chromosome. Journal of Molecular Evolution 63:676–681.

Sturgill, D., Y. Zhang, M. Parisi, and B. Oliver. 2007. Demasculinization of X chromosomes in the *Drosophila* genus. Nature 450: 233–237.

Turner, J. M. A. 2007. Meiotic sex chromosome inactivation. Development 134:1823–1831.

Turner, L. M., E. B. Chuong, and H. E. Hoekstra. 2008. Comparative analysis of testis protein evolution in rodents. Genetics 179:2075–2089.

Vicoso, B., and B. Charlesworth. 2006. Evolution on the X chromosome: unusual patterns and processes. Nature Reviews Genetics 7:645–653.

Wolfenbarger, L. L., and G. S. Wilkinson. 2001. Sex-linked expression of a sexually selected trait in the stalk-eyed fly, *Cyrtodiopsis dalmanni*. Evolution 55:103–110.

Yang, X., E. E. Schadt, S. Wang, H. Wang, A. P. Arnold, L. Ingram-Drake, T. A. Drake, et al. 2006. Tissue-specific expression and

regulation of sexually dimorphic genes in mice. Genome Research 16:995–1004.

Zauner, H., G. Begemann, M. Mari-Beffa, and A. Meyer. 2003. Differential regulation of *msx* genes in the development of the gonopodium, an intromittent organ, and of the "sword," a sexually selected trait of swordtail fishes (*Xiphophorus*). Evolution and Development 5:466–477.

Zhang, Y., D. Sturgill, M. Parisi, S. Kumar, and B. Oliver. 2007. Constraint and turnover in sex-biased gene expression in the genus *Drosophila*. Nature 450:233–238.

Zhang, Z., T. M. Hambuch, and J. Parsch. 2004. Molecular evolution of sex-biased genes in *Drosophila*. Molecular Biology and Evolution 21:2130–2139.

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