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Sex Chromosomes and Speciation

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Sex chromosomes are peculiar. In contrast to their autosomal counterparts, sex chromosomes are inherited differently in females and males, can harbor distinct sets of genes with unusual expression profiles, often experience reduced recombination, and may degenerate relatively quickly over evolutionary time. These characteristics and others have manifold biological implications.

One implication of particular evolutionary significance is that sex chromosomes play an outsized role in speciation – the process by which one species becomes two. The most widespread and convincing evidence for this conclusion stems from two empirical patterns that characterize reproductive isolation between nascent species pairs (Coyne and Orr 1989). First, when hybrid sterility or hybrid inviability is restricted to one sex, it is almost always the heterogametic sex (Haldane 1922; Coyne 1992; Laurie 1997; Presgraves 2008). Second, hybrid dysfunction differentially maps to the X chromosome in XY species and to the Z chromosome in ZW species (Coyne and Orr 1989; Coyne 1992; Presgraves 2008). These "two rules of speciation" (Coyne and Orr 1989) excite biologists because they raise the possibility of general mechanisms responsible for the birth of new species.

This issue of *Molecular Ecology* is devoted to examining the causes and consequences of the special connection between sex chromosomes and speciation. Collectively, authors update the evidence from a variety of species, provide fresh ideas, and encourage the field to embrace composite explanations.

Which special characteristics of the sex chromosomes explain their involvement in reproductive barriers? Most work in this area has centered on elucidating the "two rules of speciation", which are focused on intrinsic postzygotic isolation. Coyne (2018) provides a historical and personal perspective on the development of ideas in the field. He organizes the potential mechanisms underlying the "two rules of speciation" into the following categories: differential gene action on a hemizygous X, differential placement of genes on the X, faster evolution of genes on the X, faster evolution of males than females, and other special aspects of the X (including disrupted inactivation during spermatogenesis). Coyne's (2018) succinct

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appraisal is that "…no single theory can explain all observations, and every theory has problems explaining some observations." Coyne (2018) also shares the series of realizations and genetic studies that culminated in the influential "two rules of speciation" book chapter (Coyne and Orr 1989). Along the way, he espouses the value of the classic literature in evolutionary genetics and laments the modern decline in scholarship.

Faster Evolution of Sequences

The unusual contributions of the sex chromosomes to reproductive isolation could simply reflect faster sequence divergence. Recessive mutations arising on the X[Z] chromosome are immediately exposed to selection in the hemizygous sex, whereas autosomal recessives are initially masked in heterozygotes. This difference can lead to a higher fixation rate of new adaptive mutations on the X[Z]. Charlesworth et al. (2018) review this theoretical prediction and note its sensitivity to many parameters (including the degree of dominance, sexual antagonism, selection at linked sites, the proportion of weakly deleterious mutations, starting mutation frequencies, contrasting mutation rates in females and males, and differences in effective population size between the X[Z] and the autosomes). Updating a literature with mixed support for faster-X evolution, Charlesworth et al. (2018) argue that X-linkage indeed increases the divergence rate at functional sites (and decreases the rate at non-functional sites), at least in *Drosophila melanogaster* and closely related species. The primary cause of these adaptive faster-X effects is inferred to be a higher fixation rate of beneficial recessives, though the challenge of confounding explanations is acknowledged.

Enriching the faster-X discussion, Irwin (2018) synthesizes theory concerning sex chromosome evolution and its impact on speciation in species with ZW sex determination. As in XY systems, selection favoring recessive adaptive mutations and relaxed selection against weakly deleterious variants are both expected to elevate divergence on the Z. Irwin (2018) highlights the potential for sexually antagonistic traits, which should map preferentially to the sex chromosomes, to generate selection for mutations involved in mating preference. Comparing within-species polymorphism to between-species differentiation, Irwin (2018) estimates that the ratio of effective population sizes on the Z and the autosomes ranges widely among bird species (from 0.135-0.806). He suggests that this observation, along with elevated differentiation on the Z, is attributable to a higher frequency or strength of positive selection on this chromosome.

Faster Evolution of Gene Expression

Faster divergence at functional X[Z]-linked sequences predicts faster divergence of X[Z]-linked gene expression, a hypothesis with some empirical support. Llopart (2018) reports fresh evidence from *Drosophila santomea* and *D. yakuba* that positive selection elevates expression evolution for genes on the X. Llopart (2018) shows that noncoding sequences upstream of X-linked genes exhibit higher ratios of between-species divergence to within-species polymorphism than do putatively neutral short introns or synonymous sites. In contrast, noncoding sequences upstream of autosomal genes exhibit lower divergence/polymorphism ratios. The apparent enrichment of adaptive regulatory substitutions on the X

is strongest for genes with male-biased expression, as predicted by the faster-X theory (Charlesworth et al. 2018).

Other processes could also accelerate evolution of expression on the X chromosome. Filatov (2018) argues that in species with recently evolved gene-rich sex chromosomes, Y degeneration and associated evolution of dosage compensation on the X chromosome can be fast enough to proceed in a species-specific manner. He further argues that the observation of Haldane's rule and/or the large X-effect in species with young Y chromosomes that have yet to fully degenerate limits the generality of explanations based on hemizygosity. Focusing on two closely related species of the flowering plants, *Silene latifolia* and *S. doica*, with recently evolved sex chromosomes, Filatov (2018) reveals higher divergence in expression at X-linked gametologs with degenerate Y copies. This finding – the first demonstration of faster-X expression evolution in plants – indicates that species-specific degeneration of recently evolved Y chromosomes and compensatory expression evolution of X-linked gametologs can lead to sex-linked incompatibilities in hybrids, even on short timescales. If genes located on sex chromosomes experience faster sequence and/or expression evolution than their autosomal counterparts, there should also be consequences for species-specific organismal phenotypes. To examine this possibility, Liu and Karrenberg (2018) genetically dissect morphological, phenological, and life-history differences between *S. latifolia* and *S. dioica*. The authors find that the sex chromosomes harbor an excess of quantitative trait loci (QTL), suggesting that sex chromosomes can be hotspots for species differences, some of which could be related to speciation.

Cutter (2018) showcases the promise of another emerging model system: nematode roundworms from the genus *Caenorhabditis*. Multiple, partially inter-fertile species pairs have been recently discovered, enabling reproductive isolation to be dissected genetically across a range of evolutionary timescales. Early work on the genetics and genomics of hybrid dysfunction have revealed large X-effects and implicated novel molecular mechanisms. For instance, aberrant expression of X-encoded small RNAs is associated with developmental problems during spermatogenesis in inter-species hybrids, suggesting incompatibilities in the regulation of small RNAs.

Selfish Genetic Elements and Genome Instability

Selfish genetic elements that compete for transmission provide an alternative explanation for the role of sex chromosomes in reproductive isolation. Patten (2018) reviews the history of a model focused on meiotic drive (post-segregational bias, strictly speaking) that was initially dismissed but has recently gained traction. Because X and Y chromosomes do not recombine with one another, they are susceptible to the evolution of multi-locus drive systems – involving, for example, separate drive, target, and modifier loci – which can in turn trigger evolutionary arms races. Under this model, for instance, the X can evolve drive alleles that favor its transmission during spermatogenesis but elicit the evolution of suppressors on the Y (to avoid being killed) and on the autosomes (to restore the sex ratio). The resulting co-evolutionary arms race can lead to the build-up of otherwise cryptic (suppressed) drive systems within species that become unmasked in hybrids, where incompatible combinations of alleles reduce fertility. Patten (2018) summarizes the growing

empirical evidence for this model (including discoveries of cryptic X-linked drivers that also cause incompatibility in hybrids) while emphasizing the contribution of the X to speciation via other forms of intragenomic conflict (including sexual and parental antagonism). Building on this theme, O'Neill and O'Neill (2018) discuss the myriad ways selfish evolution of the sex chromosomes compromises genomic stability. Focusing on mammals, the authors describe several examples of rapidly diversifying copy number variants (CNVs) in repetitive DNAs on the sex chromosomes that could contribute to reproductive isolation.

Barriers to Gene Flow in Nature

Like controlled crosses in the laboratory, species that mate in nature provide clues about the genetic determinants of speciation. If lineages hybridize during species formation, mutations that reduce hybrid fitness should be exchanged less frequently than the remainder of the genome, as should variants linked to these mutations. This logic can be used to find loci responsible for reproductive isolation by scanning genomes for elevated differentiation among nascent species that currently hybridize or did so in the past. The disproportionate contribution of sex chromosomes to reproductive barriers therefore predicts that these chromosomes will be enriched for high-differentiation regions.

Presgraves (2018) provides compelling evidence in support of this prediction. By amalgamating available population genomic data from a wide variety of taxa, Presgraves (2018) shows that F_{st} – the most common measure of population differentiation – is routinely higher on the X[Z] chromosome than on the autosomes. But this pattern need not reflect selection against gene flow on the sex chromosomes, the author cautions. Higher differentiation on sex chromosomes is expected under standard assumptions and, even beyond the standard expectations, a wide range of population genetic circumstances can cause excess X-linked differentiation. On top of sex-biased migration, heightened susceptibility to demographic processes that reduce effective population size and to selection at linked sites can explain excess differentiation on the X[Z]. Presgraves (2018) advocates model-based comparisons of competing scenarios to determine the extent to which this widespread pattern is connected to speciation.

Several additional contributions highlight the challenge of considering demographic history when comparing population differentiation on the X and the autosomes. Van Belleghem et al. (2018) analyze more than 200 whole genome sequences collected from a total of 36 populations of the butterfly species *Heliconius erato* and *H. pelmomene*. The authors find higher absolute differentiation on the Z chromosome. However, simulations reveal that this pattern can be partly explained by population expansion, demonstrating that absolute (as well as relative) measures of differentiation can be shaped by population size change. At the same time, sympatric and parapatric populations of the two species have higher Z/autosome divergence ratios than allopatric populations, suggesting a lower rate of gene flow on the Z chromosome.

Moran et al. (2018) characterize RADSeq variation along a transect of two species of *Teleogryllus* crickets that represent a rare exception to Haldane's rule. Between-species differentiation is higher on the X compared to the autosomes, with a particular spike

between sympatric populations. X-linked loci are more variable than autosomal loci within populations. The authors argue that inferred population expansions do not explain these patterns, instead viewing them as consistent with a special role for the X in reproductive isolation.

Steinrücken et al. (2018) revisit evidence for gene flow between Neanderthals and modern humans. Building on their earlier approach for reconstructing demographic history, Steinrücken et al. (2018) present a new model-based method for inferring admixed ancestry along chromosomes. Applying this demography-informed strategy to population genomic data, the authors confirm that the human X harbors relatively less Neanderthal ancestry than autosomes. After investigating genomic correlates of admixture, Steinrücken et al. (2018) conclude that selection against gene flow stems from a higher load of deleterious mutations in Neanderthals and not hybrid incompatibilities.

Evolution of Sex Chromosome Systems

Several characteristics that predispose sex chromosomes to their special role in speciation arise from their function in sex determination. Consequently, the tempo with which sex determination systems and correlated traits evolve could shape rates of speciation across phylogenies. Conducting phylogenetic comparative analyses of data from teleost fish, squamate reptiles, and amphibians, Pennell et al. (2018) infer a bias in transitions from environmental to chromosomal sex determination. The authors also estimate that transitions between homomorphic and heteromorphic sex chromosomes occur at similar rates, providing context for reports that reproductive isolation evolves faster among species with heteromorphic sex chromosomes.

Ploidy is a key variable in sex chromosome evolution. Theory that compares expected patterns of gene flow on the sex chromosomes and the autosomes focuses on diploids (for obvious reasons). As Ghenu et al. (2018) point out, in the roughly 20% of animal species that are haplo-diploid, “the whole genome behaves similarly to the X/Z chromosomes of diploids”. Motivated by an unusual hybrid population of wood ants – in which hybrid males die before reaching adulthood but hybrid females enjoy increased survivorship – the authors present a mathematical model that combines hybrid incompatibility, heterozygote advantage, and assortative mating. Ghenu et al. (2018) uncover a complex fitness landscape with multiple equilibria. For diploid systems, these results are consistent with contrasting dynamics for sex chromosomes and autosomes, including unique signatures of sexual antagonism and more efficient removal of hybrid incompatibilities on the X.

Lessons and Recommendations

The 15 articles in this special issue of *Molecular Ecology* – which embody a diverse collection of approaches and study systems – offer valuable lessons about the relationship between sex chromosomes and speciation.

One message is that sex chromosomes appear to generate reproductive isolation for more than one reason. There is convincing evidence that both sequences and expression levels diverge faster when genes are X-linked, at least for some species pairs. The unusual

susceptibility of the X chromosome to the invasion and accumulation of selfish genetic elements primes it for intra-genomic conflicts that can lead to hybrid dysfunction. Finally, across broad phylogenetic timescales, species show the ability to transition between alternative sex chromosome systems, perhaps setting the stage for differences in speciation rates among clades.

Another point of consensus is that genomic differentiation among species pairs sampled in nature is higher on the X[Z] than on the autosomes. This pattern could indicate stronger selection against gene flow on the X[Z] because of its important contributions to reproductive isolation. But direct evidence for this inference remains limited. In practice, a variety of confounding factors – especially disparities in effective population size between sex chromosomes and autosomes – make it problematic to interpret elevated differentiation as a signature of reproductive isolation.

Moving forward, there are several opportunities to accelerate progress in this area. First, viewing the connection between sex chromosomes and reproductive isolation as a composite result of many factors (rather than one or the other) could usefully shift how the field looks for underlying mechanisms. Second, new analytical methods are needed that can distinguish signatures of reduced gene flow from alternative explanations. Third, it is now clear that transitions between sex determination systems and between sex chromosome systems occur more frequently over phylogenetic timescales than previously appreciated, but the contribution of this turnover to heterogeneity in speciation rates remains to be tested. Finally, systems in which mechanisms of reproductive isolation can be unraveled *and* natural hybridization can be measured offer the best prospects for meaningfully connecting causes and consequences of sex chromosomes as hotspots of speciation.

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