Resetting the rules: Sex chromosome turnover as an evolutionary escape from mitonuclear conflict

Rachel L. Moran[1*]

1. Department of Ecology & Evolution, University of Chicago, Chicago, IL

*Corresponding author, rmoran1@uchicago.edu

Abstract

Life's diversity depends on both the stability and flexibility of inheritance systems. Mitochondrial and nuclear genomes must cooperate to sustain oxidative phosphorylation and cellular metabolism, yet their distinct inheritance routes can generate evolutionary conflict. Sex chromosomes may modulate these conflicts by biasing transmission of nuclear genes toward one sex. Here I synthesize theory and comparative evidence to propose that turnover in sex-determining systems, including the gain, loss, or replacement of X, Y, Z, or W chromosomes, acts as an evolutionary "escape hatch'' from persistent mitonuclear conflict. When nuclear-encoded mitochondrial (N-mt) genes become linked to non-recombining sex-linked regions, compensatory coevolution with maternally inherited mitochondria may be altered, potentially contributing to sex-biased incompatibilities. Subsequent turnover or recombination restoration may release these loci, reshaping the genomic context of conflict and generating cycles of amplification and relief. Evidence from animals, plants, and other systems highlights possible genomic and hybrid-zone signatures consistent with these dynamics, while also underscoring alternative mechanisms and important empirical gaps. Viewing sex chromosome turnover through the lens of cytonuclear interactions offers a framework for understanding how shifts in inheritance architecture may contribute to reproductive isolation, genomic divergence and, in some clades, diversification.

Keywords

Sex chromosome turnover, Cytonuclear conflict, Inheritance asymmetry, Genomic conflict, Hybridization and reproductive isolation, Diversification and macroevolution, Mitochondrial sweeps

Key Points

- **Inheritance architectures evolve and can reshape patterns of genomic interaction.** Sex chromosome turnover alters nuclear–cytoplasmic co-transmission, potentially changing the context for mitonuclear coadaptation and the evolution of reproductive barriers.
- **Mitonuclear conflict may be dynamic rather than static.** When nuclear-encoded mitochondrial (N-mt) genes become linked to young non-recombining sex-linked strata ("entrapment"), compensatory evolution may be altered; subsequent turnover or recombination restoration may release these loci, creating cycles of conflict amplification and relief.
- **Turnover history may influence the strength and sex-bias of hybrid incompatibilities.** Stable XY and ZW systems often show long-standing sex-linked signatures of genomic conflict, whereas systems with recurrent sex chromosome turnover may experience more transient, lineage-specific restructuring of mitonuclear interactions.
- **Comparative genomics provides emerging evidence for turnover-associated restructuring of mitonuclear interactions.** Studies in fishes, amphibians, and some invertebrates suggest that changes in sex determining regions can alter the genomic context of N-mt loci, while plants and endosymbiont-driven systems offer conceptual parallels for broader cytonuclear conflict.
- **Hybrid zones provide tractable systems for testing the escape-hatch hypothesis.** Mito-aware genomic clines, sex-differentiated coverage, and physiological assays can help distinguish localized mitonuclear incompatibilities from alternative explanations, including autosomal Dobzhansky-Muller incompatibilities, meiotic drive, or genome-wide maternal sweeps.
- **Sex chromosome turnover may connect microevolutionary conflict to broader patterns of diversification in some clades.** Although evidence remains limited, turnover-driven restructuring of inheritance architecture may contribute to lineage divergence by altering recombination, genomic conflict, and the opportunity for reproductive isolation.

Introduction

Biodiversity reflects not only ecological opportunity and environmental context, but also the genomic architectures of inheritance that shape how organisms evolve (Hill 2014, 2019, Rand & Mossman 2020). Every lineage inherits a framework of recombination, cytoplasmic transmission, and sex determination that influences how genes interact across generations and how adaptation, conflict, and reproductive isolation emerge (Payseur et al. 2018). These inheritance architectures are themselves evolutionarily

dynamic: the origin, modification. and turnover of sex chromosomes can restructure patterns of genomic linkage and co-transmission, altering the context for coevolution among interacting genes (Vicoso 2019). Understanding how inheritance systems evolve may therefore help explain variation in evolutionary trajectories across lineages, including differences in the tempo of adaptation, conflict, and lineage divergence. By reshaping which genes are co-inherited and how selection acts on them, changes in inheritance architecture provide an underexplored mechanisms through which genomic evolution may contribute to broader patterns of biodiversity (El Taher et al. 2021).

Ecological opportunity, sexual selection, and developmental constraint have long been invoked to explain uneven patterns of diversification across clades (e.g., Schluter 2000, Brakefield 2006, Seehausen 2006). Yet variation in biodiversity also reflects a less appreciated dimension of evolution: the architecture of inheritance itself. Here, inheritance architecture- refers to the recombinational and transmission systems that govern how genes are co-inherited across generations, including sex determination, recombination suppression, and cytoplasmic inheritance (Barton & Charlesworth 1998, Rice 2013, Bachtrog et al. 2014, Greiner et al. 2015). These architectures shape not only how selection acts, but where evolutionary conflicts arise and how they are resolved. Over deep time, inheritance architectures are far from static. Polyploidy, endosymbiosis, and horizontal transfer have repeatedly rewritten the rules of genomic cooperation. In animals and many plants, turnover in sex determining systems provides a recurrent, lineage-specific mechanism for doing so. Each replacement of a sex determining region (SDR) redraws the map of sex-biased inheritance, altering linkage relationships between thousands of nuclear loci and cytoplasmic genomes. Comparative genomic data across diverse taxa now reveal that such turnover is far more common than once assumed, occurring on the timesclaes of only a few million years in some fishes and amphibians (Kitano & Peichel 2012, Gammerdinger & Kocher 2018, Jeffries et al. 2018, Evans et al. 2024), raising the possibility that repeated restricting of inheritance systems is itself an important contributor to macroevolutionary diversification.

Because inheritance asymmetries determine which genes share evolutionary fate, they also define where conflict can emerge between genomes. Mitochondrial and nuclear genomes are a classic example: although both are required for oxidative phosphorylation and core cellular metabolism, they typically follow different transmission routes and therefore experience different selective environments. This asymmetry creates the potential for mitonuclear conflict, in which coadaptation is disrupted and fitness costs emerge through physiological dysfunction, sterility, or hybrid breakdown (Burton & Barreto 2012, Rice 2013, Hill 2019, Havird et al. 2019, Rand & Mossman 2020). One mechanistically explicit route by which these conflicts may be amplified is when nuclear-encoded mitochondrial (N-mt) genes become

linked to sex chromosomes, which bias transmission toward one sex and therefore one cytoplasmic lineage.

In this Review, I propose that sex chromosome turnover can dynamically reshape the genomic landscape of mitonuclear conflict by repeatedly altering which N-mt genes (i.e., nuclear genes whose products function in mitochondria - not to be confused with NUMTs, nuclear mitochondrial DNA insertions that are largely non-functional and not considered here) become sex-linked or return to autosomal inheritance. Here, I use "entrapment" to refer to the persistent association of N-mt genes with sex-linked inheritance through recombination suppression around sex-determining regions, which alters their co-inheritance with mtDNA and can reshape patterns of coadaptation or conflict. Entrapment does not require novel mutations on the sex chromosome. Rather, reduced recombination may limit the ability of N-mt loci to track mitochondrial evolution efficiently, allowing mtDNA-conditional fitness mismatches to persist or accumulate following turnover, introgression, or environmental change. Building on theory showing that mitonuclear conflict can shape recombination, sex linkage, and, even mitochondrial transmission modes within otherwise stable inheritance systems (Rice 2013, Connallon et al. 2018, Havird et al. 2019, Radzvilavicius et al. 2021), this Review synthesizes these established ideas with sex chromosome turnover theory to propose how turnover may repeatedly restructure the genomic context in which cytonuclear incompatibilities evolve.

I present an "escape-hatch'' framework in which new sex determining regions reset the genomic location and intensity of conflict, generating predicted episodic pulses of coadaptation and incompatibility that may leave detectable genomic signatures. Under this model, turnover not only resolves conflict, but may also relocate or amplify it by creating new linkage relationships between sex-determining regions and N-mt genes. Any fitness costs associated with entrapment are expected to be balanced against the evolutionary forces that favor turnover itself, including sex-ratio distortion, sexual antagonism, drift in small populations, or transient advantages of novel sex-determining alleles. As a result, turnover need not be universally beneficial to persist or spread. At the same time, turnover may also reconfigure opportunities for mitonuclear coadaptation by altering the degree of co-transmission between mtDNA and interacting nuclear loci. Depending on genomic context, tighter linkage may stabilize coadapted combinations, whereas release to autosomal inheritance may restore independent evolutionary trajectories and facilitate compensatory coevolution (Hill 2014). As a consequence, classic speciation patterns such as Haldane's rule and the large-X/Z effect may vary with the age and identity of sex chromosomes. The strength of these effects is expected to depend on the genomic extent of sex linkage and may be minimal in systems where sex determination is governed by very small SDR or single-locus sex determiner. By

linking sex chromosome turnover to mitonuclear coevolution, this framework proposes that changes in inheritance architecture can act as conditional contributors to reproductive isolation and diversification in lineages where turnover reshapes sex-linked genomic interactions. Although no system yet documents the complete temporal sequence of capture, entrapment, and release, recent work in darters (Radcliffe et al. 2025) integrates sex chromosome turnover, sex-linked localization of nuclear-encoded mitochondrial genes, cytoplasmic-background–dependent transmission distortion, and reduced introgression within a single hybridizing lineage, providing one of the strongest empirical foundations for the framework proposed here.

Mitonuclear coadaptation, conflict, and sex chromosomes

Mitochondria are central not only to ATP production through oxidative phosphorylation (OXPHOS) but also to heat generation, apoptosis, calcium homeostasis, steroid synthesis, and production of reactive oxygen species (Rand et al. 2004, Ballard & Pichaud 2014). These functions depend on tight coordination between maternally inherited mtDNA and more than a thousand nuclear-encoded genes whose protein products function in mitochondrial processes such as oxidative phosphorylation, mitochondrial ribosome assembly, and mitochondrial protein import (Hill 2019). Sex linkage may therefore influence not only conflict but also the efficiency of mitonuclear coadaptation by altering the co-inheritance of interacting loci (Hill 2014). This cooperation persists despite distinct inheritance routes: mtDNA is typically inherited through the egg cytoplasm, whereas nuclear loci recombine biparentally. Such asymmetry can generate conflict whenever selection on mtDNA diverges from that on the nuclear background or when hybridization brings together incompatible mito-nuclear combinations (Burton & Barreto 2012, Havird et al. 2019, Rand & Mossman 2020). Because mtDNA is maternally inherited, mutations that are neutral or beneficial in females can spread even when they impose fitness costs on males ("Mother's Curse"), while compensatory mutations must arise in nuclear genes to restore coadaptation (Gemmell et al. 2004). Even under a fixed inheritance architecture, such mitonuclear coadaptation cycles impose a sizable, male-biased mitochondrial load that is strongly dependent on effective population size (Ne), providing a quantitative baseline for transient male fitness costs against which the turnover-driven pulses proposed here can be evaluated (Connallon et al. 2018). Hybridization between divergent lineages can further disrupt these pairs, producing reduced fitness, sex-biased sterility, or energetic inefficiency, phenomena documented in copepods, mussels, *Drosophila*, and fishes (Burton et al. 2006, Ellison & Burton 2008, Saunier et al. 2014, Hill 2014, 2019).

Sex chromosomes intersect with these dynamics because they bias the co-transmission of nuclear loci with mtDNA. Z chromosomes spend two-thirds of their evolutionary history in males, X chromosomes

two-thirds in females, while W and Y are confined to the heterogametic sex, with the W co-inherited with mtDNA and the Y entirely decoupled from it (Mank 2012). When N-mt genes become linked to low-recombination sex-linked strata, their inheritance patterns can shift in ways that may alter the efficacy of compensatory evolution and increase the potential for mitonuclear mismatch. Such interactions may contribute to patterns of hybrid disfunction, including sex-biased sterility or inviability, and represent one potential mechanism contributing to broader patterns such as Haldane's rule (Haldane 1922, Orr 1997) and the large-X/Z effect (Ellegren 2009, Llopart 2012). Because sex chromosome turnover changes which genomic regions experience sex-biased transmission, it can repeatedly restructure the evolutionary context in which mitonuclear coadaptation unfolds.

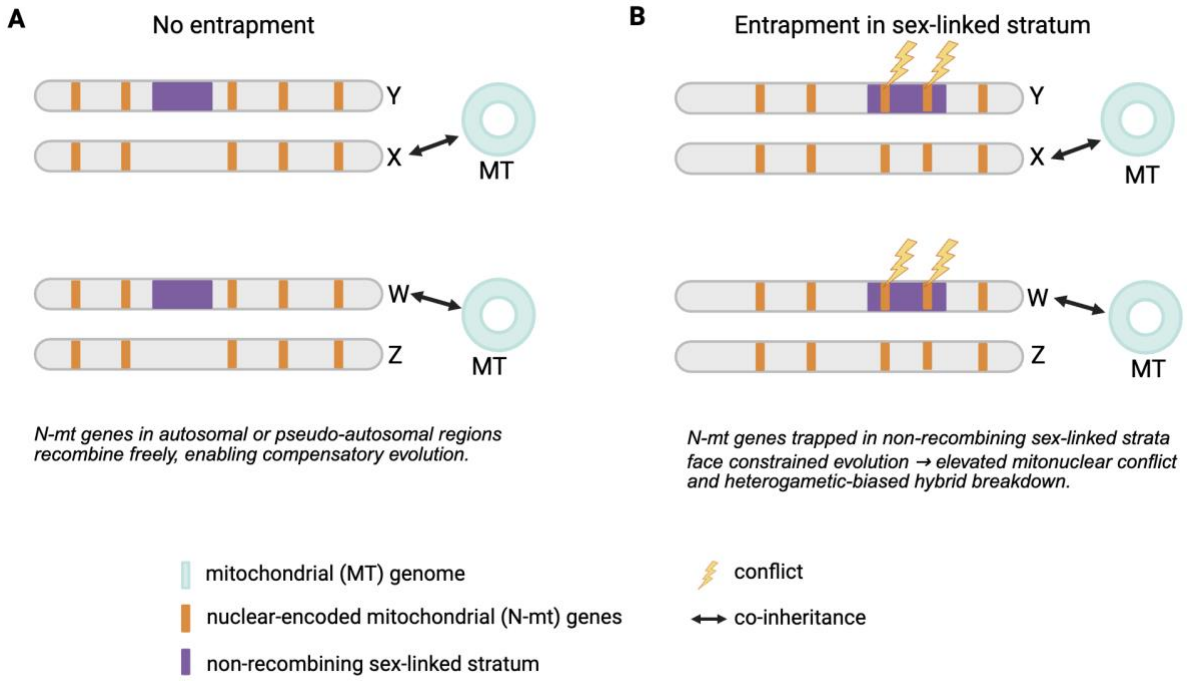


Figure 1. Entrapment, not enrichment: how sex-linked strata can bias mitonuclear loci.
Schematic chromosomes illustrate two genomic contexts for N-mt genes (orange). (A) N-mt genes within autosomal or pseudo-autosomal regions recombine freely and can track mitochondrial evolution, minimizing mitonuclear conflict. (B) Local linkage of N-mt genes in a non-recombining sex-linked stratum (purple) may constrain compensatory evolution by reducing opportunities for favorable mito-nuclear combinations to reassort (Princepe & de Aguiar 2024), This can increase the persistence of mtDNA-conditional fitness mismatches, potentially intensifying mitonuclear conflict (lightning bolts) and contributing to heterogametic-biased hybrid breakdown when mtDNA-conditional effects are demonstrated. MT = mitochondrial genome (light blue).

Insights from stable XY and ZW systems

Across the tree of life, certain lineages have maintained the same sex chromosome systems for tens to hundreds of millions of years (Graves 2016, Vicoso 2019). These *stable* architectures offer a view of how long-term genomic arrangements shape mitonuclear dynamics once turnover has ceased. In such systems, the consequences of long-term recombination suppression can become deeply embedded: sex-linked strata commonly accumulate degeneration, while meiotic drive and dosage-compensatory responses are reported but vary substantially across clades (Charlesworth 1991, Bachtrog 2013). Although mammals and birds are the best-studied examples, similar principles emerge in some insect and nematode lineages where heterogamety has remained stable over long evolutionary timescales (Bull 1983, Charlesworth 2017).

Stable XY systems

In taxa with stable XY systems, the X chromosome recombines in the homogametic sex but is hemizygous in the heterogametic sex, whereas the Y is often gene-poor and decoupled from mitochondrial inheritance (Bachtrog 2013). Across mammals, N-mt genes are often underrepresented on the X relative to autosomes, a genomic pattern consistent with sex-specific selective pressures on mito-nuclear coadaptation, though the mechanisms generating this bias remain unresolved (Drown et al. 2012, Dean et al. 2014). Nevertheless, heterogametic males often experience hybrid dysfunction (**Table 1**), suggesting that mitonuclear mismatch can still arise through other routes. The observed paucity of N-mt genes on the mammalian X is consistent with models in which mitonuclear conflict favors inheritance architectures that reduce persistent sex linkage, including sex-independent segregation or altered recombination dynamics; related models also predict sex-specific selection on recombination and, context-dependently, paternal leakage (i.e., the rare transmission of mitochondria through sperm, which can transiently increase co-transmission between male nuclear alleles and mtDNA; Radzvilavicius et al. 2021). Comparable patterns occur in long-conserved XY systems of *Drosophila*, where mito-sensitive genes are preferentially autosomal and male-biased sterility is pervasive (Gallach et al. 2010, Lindsley et al. 2013, Rogell et al. 2014, Ågren et al. 2020). In nematodes, where X-autosome balance governs sex, N-mt loci are similarly under-represented on the X, hinting at parallel selective pressures to decouple mitochondria from sex-linked inheritance (Dean et al. 2014).

Stable ZW systems

In taxa with stable ZW systems such as birds, the Z spends two-thirds of its time in males, while the W is maternally co-inherited with mtDNA. The avian Z remains gene-rich relative to the highly degenerated W and retains functional loci, including some N-mt genes. In birds and other ZW taxa, hybrid dysfunction often disproportionately affects the heterogametic sex (females), consistent with Haldane's rule (Ottenburghs 2022). Several avian hybrid zones show coincident clines of mtDNA and Z-linked alleles (Lopez et al. 2021, Del-Rio et al. 2022), patterns consistent with (i) mitonuclear linkage between mtDNA and N-mt loci embedded in Z-linked low-recombination strata or (ii) W-linked meiotic drive causing mitochondrial sweeps (Irwin 2025) (**Table 1**). Because female-biased hybrid breakdown can also arise from intrinsic W–Z genic incompatibilities unrelated to mitochondria, we use "entrapment'' here only when the fitness effects of sex-linked alleles depend on the mitochondrial haplotype with which they co-occur. Distinguishing these alternatives requires reciprocal crosses, mito-aware genomic-cline analyses (e.g., local ancestry near SDR versus genome-wide), and direct assays of mitochondrial performance in reciprocal hybrids (see *Testing the escape-hatch hypothesis across scales* below).

Related cytonuclear conflicts occur outside mitochondria-focused systems. In Lepidoptera, the maternally inherited W chromosome is often enriched in repetitive elements and may carry sequences derived from cytoplasmic endosymbionts or meiotic-drive elements (Fraïsse et al. 2017, Dalíková et al. 2017). Many butterflies and moths exhibit female-biased hybrid sterility and tight mito-W associations consistent with historical drive or mitonuclear linkage. In some crustaceans (e.g., *Armadillidium*), bacterial endosymbionts such as *Wolbachia* can feminize genetic males, altering the relationship between chromosomal sex determination and cytoplasmic inheritance (Cordaux et al. 2011). In flowering plants, cytonuclear conflict is well documented through cytoplasmic male sterility (CMS) and nuclear restorers, although these systems typically occur in gynodioecious rather than dioecious species and generally operate outside canonical sex chromosome systems. These examples are not direct equivalents of mitonuclear entrapment, but they illustrate the broader principle that cytoplasmic inheritance can shape conflict and coadaptation with nuclear genomes and influence the evolutionary context in which sex-determining systems arise and diversify.

Takeaways

Stable systems show that cytonuclear conflict can leave persistent, sex-linked signatures, but their ancient architectures limit leverage to ask how *changes* in linkage reshape conflict dynamics. Instead, they provide a comparative baseline for how long-term sex linkage can shape genomic degeneration, dosage

evolution, and the distribution of nuclear-encoded mitochondrial loci, against which more labile systems can be evaluated.

Table 1. Comparative predictions for mitonuclear conflict across sex chromosome systems. Predictions for the strength, persistence, and sex-bias of mitonuclear conflict across stable and labile sex chromosome systems, including turnover that preserves heterogamety (XY→XY, ZW→ZW) and turnover that reverses heterogamety (XY↔ZW). Row summarize representative taxa or taxonomic groups, genomic context (e.g. age of the SDR, and degree of N-mt linkage), expected temporal dynamics of conflict, predicted patterns of hybrid dysfunction, and genomic signatures associated with sex-linked barriers. Stable systems may exhibit more persistent conflict shaped by long-term genomic sorting, whereas labile systems are expected to experience more episodic and lineage-specific conflict as SDRs shift or heterogamety changes. ZW systems (purple) may show stronger maternal-haplotype asymmetries because the W chromosome is co-inherited with mitochondria, whereas XY systems (blue) may show male-biased hybrid dysfunction when newly formed sex-linked strata become linked to N-mt loci.

Comparative predictions for mitonuclear conflict across sex-chromosome systems

Axis	Labile XY→XY	Labile ZW→ZW	Labile XY↔ZW	Stable XY	Stable ZW
Exemplars	Ranid frogs (Jeffries et al. 2018), percid fishes (Kuhl et al. 2024, Radcliffe et al. 2025), salmonids (Phillips 2013)	Lepidoptera (multiple independent W origins, Han et al. 2024; neo-Z/neo-W systems, Höök et al. 2024)	Geckos (Gamble et al. 2015), tilapiine cichilds (Cnaani et al. 2008), Tanganyikan cichlids (El Taher et al. 2021), snakes (Gamble et al. 2017), dioecious *Silene* (section *Otites*) (Balounova et al. 2019)	Mammals (Rice 1996), *Drosophila* (Bachtrog 2013)	Birds (Ottenburghs 2022), varanid reptiles (Rovatsos et al. 2019), characiform fishes (Yano et al. 2021)
State / age	Turnover in sex-chromosome identity; male heterogamety retained	Turnover in sex-chromosome identity; female heterogamety retained	Turnover reverses heterogamety; XY and ZW systems alternate	Ancient, conserved XY; long-term recombination suppression	Ancient, conserved ZW; long-term recombination suppression
N-mt context	New SDRs may become linked to different N-mt loci; Y remains decoupled from mtDNA	New SDRs may become linked to different N-mt loci; W remains maternally co-inherited with mtDNA	Major reset of sex-biased transmission; W–mtDNA co-inheritance can be gained or lost	X often underrepresented for N-mt loci; Y decoupled from mtDNA	Z remains gene-rich relative to W; W co-inherited with mtDNA
Conflict expectation	Episodic conflict after new linkage; potential relief when SDRs move	Episodic conflict after new linkage; maternal asymmetry maintained	Major restructuring of inheritance asymmetry; potential reversal of sex-biased conflict	Persistent conflict; long-term genomic sorting reduces N-mt linkage	Persistent female-biased asymmetry; possible W-drive and mito-W co-inheritance effects
Hybrid dysfunction	Episodic **male-biased** hybrid breakdown	Episodic **female-biased** hybrid breakdown	Lineage-specific; sex bias may reverse after heterogametic switches	**Male-biased** hybrid dysfunction; large-X effect	**Female-biased** hybrid dysfunction; large-Z effect
Turnover dynamics	Documented XY→XY or XY→polygenic transitions	Documented ZW→ZW or ZW→polygenic transitions	Documented XY↔ZW switches; heterogamety itself changes	Rare or absent	Rare or absent
Genomic signatures	Sharp local clines near SDRs; transient sex-linked barriers; limited strata	Emerging neo-sex strata; test mtDNA-conditional effects vs W-drive	Shifts in sex-biased ancestry, mtDNA association, or hybrid dysfunction	Persistent X-linked barriers; weak mito-X coupling	Coincident mtDNA and Z-linked clines; persistent Z effect

Note: Female-biased dysfunction in ZW clades can also arise from intrinsic Z-W genic incompatibilities independent of mitochondria. Patterns of mtDNA-sex chromosome association should therefore be interpreted cautiously and evaluated alongside reciprocal crosses, genomic cline analyses, and direct assays of mitochondrial performance (see Comparative genomics and new opportunities for diagnostics).

Labile systems as natural experiments

In contrast to the long-entrenched XY and ZW systems of mammals and birds, many lineages spanning fishes, amphibians, insects, crustaceans, and plants exhibit diverse and evolutionarily dynamic sex determining architectures. Across these groups, sex determination can be reshaped through turnover, chromosomal fusions, and XY↔ZW transitions, or repeated independent origins of sexdetermining systems, creating natural experiments for understanding how shifting linkage relationships may modulate

mitonuclear coadaptation and conflict. This lability reveals that sex chromosome turnover is not a vertebrate peculiarity but a recurrent evolutionary strategy for reconfiguring inheritance across eukaryotes.

Repeated sex chromosome turnover and compound systems in fishes and insects

Teleost fishes provide well-documented examples of repeated sex chromosome turnover. Multiple lineages, including cichlids, sticklebacks, salmonids, medaka, and darters, show repeated transitions in sex determining regions. These transitions are often accompanied by chromosome fusions and, in some cases, XY↔ZW switches over relatively short evolutionary timescales (e.g., <15–20 Myr; Kitano & Peichel 2012, Lubieniecki et al. 2015, Myosho et al. 2015, El Taher et al. 2021, Radcliffe et al. 2025). Cichlids are among the most dynamic examples: East African radiations harbor over a dozen independent XY and ZW systems distributed across at least ten linkage groups, including compound systems involving W, Y, and B chromosomes (Gammerdinger & Kocher 2018). B chromosomes are supernumerary, often dispensable, chromosomes that can acquire sex-determining or meiotic-drive functions, thereby interacting with primary sex chromosomes. This "hot-potato'' dynamic in which new sex-determining alleles repeatedly invade and replace older systems can generate repeated cycles of conflict and resolution (Blaser et al. 2014).

Comparable tempos occur in non-vertebrate taxa. Drosophilids frequently undergo sex chromosome-autosome fusions and neo-sex chromosome formation (Vicoso & Bachtrog 2015), while many beetles and hemipterans show repeated autosome–sex fusions and multi-sex chromosome systems (Blackmon & Demuth 2014, Blackmon et al. 2017). Together, these examples suggest that sex chromosome lability, and the resulting reshuffling of nuclear-mitochondrial linkage, is a widespread feature of rapidly diversifying clades.

Homomorphy, turnover, and cytonuclear conflict in frogs and plants

Anurans provide an intermediate pattern between highly labile and deeply differentiated sex chromosome systems. Many frog lineages retain homomorphic sex chromosomes with occasional recombination between X and Y (or Z and W), which can limit long-term degeneration and preserve flexibility in sex determining architecture. This pattern forms the basis of the "fountain-of-youth" model, in which episodic recombination rejuvenates sex chromosomes and delays divergence (Perrin 2009). Other anuran clades, including ranids and *Xenopus*, show repeated turnover, strata formation, and heterogamety transitions, indicating that recombination and replacement can jointly shape sex chromosome evolution

(Jeffries et al. 2018, Evans et al. 2024, Miura et al. 2024, Uno & Matsubara 2024). In *Xenopus*, at least seven turnovers across ~321 Myr imply long-term turnover rates of ≈0.02 events Myr^{-1} (Evans et al. 2024), while Ranidae frogs show comparable rates (~1 per 50 Myr; Jeffries et al. 2018).

Plants offer a related but mechanistically distinct perspective. In many gynodioecious angiosperms, mitochondrial mutations causing cytoplasmic male sterility (CMS) generate cytonuclear conflict by favoring female function, while nuclear restorer (*Rf*) genes evolve to suppress sterility and restore pollen production (Touzet & Meyer 2014, Renner 2014). This creates a direct and recurrent cytoplasmic–nuclear feedback loop analogous to mitonuclear conflict in animals, but it does not generally require sex chromosome linkage. Separately, repeated independent origins of dioecy and sex determining systems in lineages such as *Fragaria*, *Salix*, and section *Otites* of *Silene* demonstrate that plant sex determination has evolved repeatedly across angiosperms (Renner 2014, Balounova et al. 2019, Charlesworth 2019). Together, frogs and plants illustrate distinct evolutionary routes by which inheritance architecture can remain flexible: in frogs through recombination and recurrent turnover, and in plants through repeated origins of sex determining systems and persistent cytonuclear conflict.

Endosymbiont-driven transitions in crustaceans and other invertebrates

In crustaceans and other invertebrates, sex determination can be destabilized by maternally inherited endosymbionts. In isopods and copepods, bacterial symbionts such as *Wolbachia* and *Cardinium* can induce feminization or sex-ratio distortion, altering the selective landscape of sex determination and, in some cases, favoring the spread of new sex-determining alleles or replacement of existing systems (Rigaud et al. 1997, Bouchon 1998, Cordaux et al. 2011). Because these symbionts are transmitted through the cytoplasm, they create direct cytonuclear conflicts over host sex allocation, coupling cytoplasmic and nuclear inheritance in ways analogous to mitonuclear conflict (Charlat et al. 2007, Engelstädter & Hurst 2009). Similar symbiont-mediated sex-ratio distortion occurs across diverse arthropods, including butterflies, mites, and other insects, highlighting a broader route by which maternally inherited elements can reshape inheritance architecture and influence the evolution of sex determination (Hurst & Frost 2015, Kageyama et al. 2017).

Takeaways

Across fishes, amphibians, insects, crustaceans, and plants, sex chromosome turnover and restructuring can occur on relatively shallow evolutionary timescales in lineages with labile sex determination, often

within the window of population divergence or recent lineage splitting rather than only across deep phylogenetic timescales (Saunders 2019, Palmer et al. 2019). These genomic "resets'' can reshape the linkage context of nearby N-mt genes, creating natural experiments in cytonuclear evolution: some turnover events may generate transient mitonuclear conflict when N-mt loci become newly sex-linked, whereas others may relax or reconfigure such conflict when recombination is restored or the sex determining region shifts to a different chromosome.

Classic models of sex chromosome turnover highlight a recurring set of underlying mechanistic drivers, including sexually antagonistic selection, mutational load in non-recombining Y/W regions, genetic drift, heterochiasmy, and sex reversal (reviewed in Vicoso 2019), that jointly shape when new sex determining regions arise, when recombination is suppressed, and when existing systems are retained or replaced. These same factors are expected to influence the likelihood and strength of cytonuclear incompatibilities linked to sex chromosomes, with elevated potential for cytonuclear incompatibilities when newly formed non-recombining strata capture N-mt loci and weaker effects in homomorphic systems or when episodic recombination between sex chromosomes is maintained through sex reversal, as proposed under the fountain-of-youth model (Perrin 2009) (see **Table 2**). Together, these systems suggest that sex chromosome turnover can modify the genomic context in which incompatibilities evolve, potentially contributing to reproductive isolation in some lineages, rather than acting as a universal speciation mechanism.

Table 2. Mechanistic drivers of sex chromosome turnover and predicted cytonuclear consequences. Primary evolutionary mechanisms that generate or resolve sex chromosome turnover, grouped by how they can restructure inheritance between nuclear and cytoplasmic genomes. These mechanisms can alter the linkage relationship of N-mt genes and sex determining regions, potentially changing the strength and direction of cytonuclear conflict. Some drivers (e.g., sexually antagonistic selection, chromosomal fusion) may increase conflict potential by creating new linkage between sex determining regions and nearby N-mt loci, whereas others (e.g., mutation load, sex reversal, and polyploidy) may relax or reconfigure those associations. Example systems and key references illustrate the diversity of turnover mechanisms across diverse eukaryotic lineages.

Driver	Mechanistic basis	Predicted impact on conflict	Example systems	Key references
Sexually antagonistic selection	New SDR invades linked to sex-beneficial allele	May bring nearby N-mt loci into new sex-linked contexts, elevating conflict potential	Cichlids, guppies, willows	Kitano & Peichel 2012; Blaser et al. 2014; Pucholt et al. 2017
Mutation load ("hot-potato")	Degeneration or mutation load on Y/W may favor SDR replacement	May release previously sex-linked N-mt loci, relaxing or reconfiguring conflict	Frogs, salmonids	Charlesworth & Wall 1999; Jeffries et al. 2018
Heterochiasmy	Sex-biased recombination limits exchange in one sex	May stabilize sex-linked associations and maintain cytonuclear asymmetries	*Drosophila*, birds, mammals	Morgan 1912; Lenormand 2003; Vicoso 2019
Sex reversal / ESD	Recombination restored through sex reversal or environmental triggers	Can restore gene exchange and relax linkage-dependent conflict	Ranid frogs, reptiles	Perrin 2009; Miura et al. 2024
Chromosomal fusion	Fusion expands non-recombining region around SDR	Can bring additional N-mt loci into sex-linked linkage, creating transient conflict opportunities	Diptera, Lepidoptera, Sticklebacks	Kitano et al. 2009; Höök et al. 2024; Layana et al. 2026
Polyploidy / WGD	Genome duplication restructures nuclear-cyto interactions	May buffer or reorganize cytonuclear interactions through gene duplication	Salmonids, angiosperms	Allendorf & Thorgaard 1984; Muyle et al. 2017
Endosymbiont manipulation	Cytoplasmic sex-ratio distortion selects for host suppressors or novel sex determiners	Rewires inheritance asymmetries; may precipitate replacement or restructuring of sex determining systems	*Armadillidium vulgare*, Lepidoptera, mites	Rigaud et al. 1997; Cordaux et al. 2011; Kageyama et al. 2017

364

365

Turnover as an evolutionary "escape hatch"

Sex-chromosome turnover may function as an evolutionary escape hatch, i.e., a mechanism by which lineages reset inherited conflicts between nuclear and cytoplasmic genomes. When deleterious mitonuclear interactions are amplified because an N-mt gene becomes entrapped within a Y- or W-linked non-recombining stratum, a subsequent turnover (either restoring recombination or moving the sex-determining locus to a new chromosome) can release that locus from persistent sex-biased inheritance (**Fig. 2**). Similar "reset" processes have been proposed in other genomic contexts, such as translocation of selfish elements (Hurst 1995, Hurst & Werren 2001) or recombination restoration following neo-sex fusion decay (Perrin 2009), but here I extend the concept specifically to the resolution of cytonuclear conflict. This framework extends baseline expectations from coadaptation theory, where male load accrues under fixed linkage, by showing how turnover restructures linkage to first amplify and then relieve that load in predictable phases (Connallon et al. 2018).

Predictions

1. **Amplification phase:** Nascent non-recombining strata that capture N-mt loci produce intensified, often heterogametic-biased conflict, segregation distortion, and steep genomic clines centered on the SDR (**Fig. 2**).
2. **Relief phase:** Later turnover or recombination expansion decouples the locus from tight sex linkage, lowering conflict and eroding barriers (**Fig. 2**); this leaves a genomic "scar" characterized by attenuating introgression deficit/discordant ancestry through time.
3. **XY vs. ZW asymmetries:** Because the W co-transmits with mtDNA whereas the Y does not, ZW systems should more often exhibit persistent female-biased breakdown and mt sweeps via W-drive; XY systems may show more frequent relief via turnover if N-mt loci are purged from tight X-linkage (Table 1).
4. **Demography dependence:** Transient costs should scale with effective population size, i.e., large costs in very small and very large Ne, minimized at intermediate Ne per coadaptation theory; turnover modulates the duration and visibility of these costs by breaking or restoring tight sex-linked N-mt inheritance (Connallon et al. 2018).

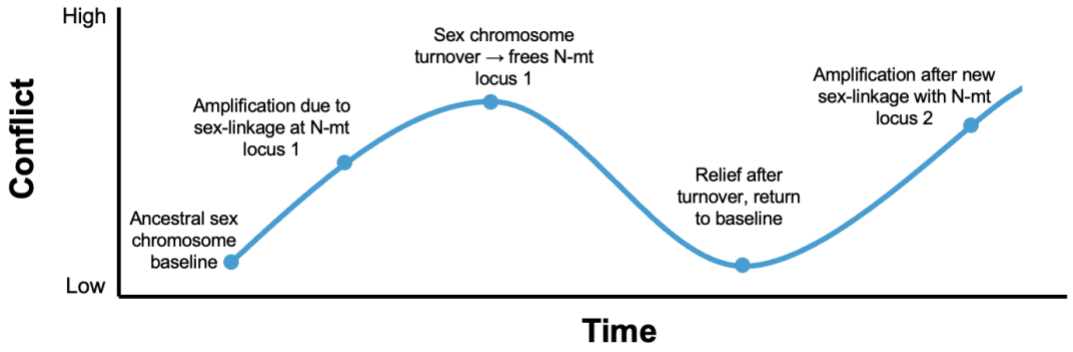


Figure 2. Turnover as an evolutionary "escape hatch." Conceptual timeline showing how cycles of sex chromosome turnover modulate the intensity of mitonuclear conflict through time. The x-axis represents evolutionary time rather than a fixed number of generations; depending on the organism and turnover mechanism, these phases may span many generations to millions of years. Conflict is low under the ancestral sex-determining region (SDR). When a turnover event establishes a new SDR that captures an N-mt locus, conflict is amplified (upslope) as compensatory evolution is constrained in the non-recombining stratum. A subsequent turnover or restoration of recombination that frees that locus from the SDR relieves conflict (downslope). If a later turnover again captures a different N-mt locus, conflict could rise again. This model predicts amplification–relief dynamics that may generate detectable pulses and localized ancestry deficits, but time-calibrated empirical tests are needed to estimate phase durations and validate this dynamic.

Alternative explanations and diagnostic contrasts

These predictions are not unique to mitonuclear entrapment. Sex-biased hybrid dysfunction and broader patterns such as Haldane's rule and the large-X/Z effect can also arise through several established mechanisms, including dominance/hemizygosity of recessive X- or Z-linked incompatibilities, autosomal Dobzhansky–Muller incompatibilities, and genome-wide maternal sweeps driven by W-linked meiotic drive or cytoplasmic endosymbionts. These alternatives can generate overlapping signatures of reproductive isolation, making mechanistic inference challenging. The key prediction distinguishing mitonuclear entrapment is mitochondrial-haplotype conditionality: fitness effects should depend on the mitochondrial haplotype background in which sex-linked alleles occur and should generate localized, sex-linked ancestry distortions rather than genome-wide cytoplasmic sweeps or purely autosomal barriers. **Table 3** summarizes these alternative mechanisms and their contrasting genomic, physiological, and temporal predictions.

Table 3. Alternative mechanisms generating sex-biased hybrid dysfunction and their diagnostic predictions. Comparative predictions of four non-mutually exclusive mechanisms that can generate sex-biased hybrid dysfunction or contribute to Haldane's rule and large-X/Z effects. Dominance/hemizygosity and autosomal Dobzhansky–Muller incompatibilities (DMIs) represent established general mechanisms, whereas mitonuclear entrapment and W-drive/endosymbiont-mediated sweeps generate distinctive cytonuclear predictions. The table highlights diagnostic differences in mitochondrial conditionality, genomic cline structure, reciprocal-cross asymmetry, and temporal dynamics that can help distinguish these mechanisms in hybrid zones.

Mechanism	Genetic basis	Expected sex bias	Genomic cline prediction	Temporal expectation	Diagnostic test
Dominance/ hemizygosity	Recessive X/Z incompatibilities exposed in heterogametic sex	Heterogametic breakdown	Elevated X/Z resistance to introgression	Accumulates gradually	Reciprocal crosses + ancestry
Autosomal DMIs	Interacting autosomal loci	Variable	Localized autosomal barriers	Accumulates with divergence	Genome-wide clines
Mitonuclear entrapment	Sex-linked N-mt × mtDNA mismatch	Often sex-biased, cross-direction-dependent	SDR-linked + mt-associated ancestry distortions	Strongest after turnover/recent linkage shifts	Reciprocal crosses + OXPHOS assays
W-drive/ endosymbionts	Cytoplasmic distortion + suppressors	Often female-biased or sex-ratio distorted	Cytoplasm-linked asymmetry	Sweep-like dynamics	Endosymbiont assays + cytoplasm replacement

From hybrid breakdown to diversity: when turnover reshapes reproductive isolation

Hybrid zones provide natural experiments for testing how sex-linked mitonuclear entrapment, alongside alternative mechanisms of hybrid dysfunction, may contribute to the formation, maintenance, or erosion of reproductive isolation through time. In taxa with stable XY systems such as mammals and *Drosophila*, hybrid breakdown typically affects the heterogametic sex (males), largely through hemizygous exposure and dosage-compensation limits rather than active mitonuclear conflict, as most nuclear-encoded mitochondrial (N-mt) loci have relocated to autosomes (Drown et al. 2012, Gallach et al. 2010; **Table 1**). In contrast, predominantly ZW systems such as birds, snakes, and many Lepidoptera often exhibit coincident mitochondrial and sex-linked clines and female-biased hybrid sterility or inviability, patterns consistent with cytonuclear incompatibilities shaped by maternal co-inheritance of mtDNA and the heterogametic sex chromosomes (Morales et al. 2018, Lopez et al. 2021, Del-Rio et al. 2022). Whether

such patterns arise from entrapment of N-mt genes in low-recombination strata or from W-linked drive and other sex-ratio distorters can be distinguished by spatial scope and temporal dynamics, as recurrent conflict between distorters and suppressors can generate rapid shifts in sex-determining architecture (Bachtrog et al. 2014, Irwin 2025; **Fig. 3**).

Lineages in which sex chromosome turnover has been documented, including some fishes, amphibians, and plants, are predicted to follow a two-phase cycle when turnover reshapes sex-linked inheritance. When new sex-determining regions capture N-mt loci, conflict may intensify and increase the likelihood of hybrid incompatibilities (the amplification phase; **Fig. 2**). Subsequent turnover or recombination restoration can decouple these loci from sex linkage, potentially relieving conflict and weakening reproductive barriers (the relief phase; **Fig. 2**). These cycles predict temporal heterogeneity in the strength and sex-bias of reproductive isolation among closely related taxa (Radcliffe et al. 2025). Homomorphic systems such as many frogs are predicted to exhibit only transient entrapment because recombination and sex reversal recurrently reset linkage (Dufresnes & Crochet 2022). The tempo and mode of postzygotic isolation therefore depend not only on sequence divergence but also on sex chromosome age and turnover history.

At broader evolutionary scales, repeated genomic resets may alter the tempo and mode of diversification by reshaping linkage relationships, recombination landscapes, and the inheritance of traits involved in reproductive isolation. Several clades with documented recurrent sex chromosome turnover, including African cichlids, darters, ranid frogs, and willows, provide useful comparative systems for testing whether repeated turnover is associated with lineage diversification, although turnover is unlikely to be the sole or dominant explanation for species richness in these groups (Kitano & Peichel 2012, Jeffries et al. 2018, Muyle et al. 2017, Radcliffe et al. 2025). Each turnover can reconfigure recombination landscapes and alter the genomic context in which reproductive incompatibilities accumulate, analogous to the repatterning events following whole-genome duplication, and may contribute to diversification alongside ecological opportunity, life history, and demographic context. Comparative phylogenetic analyses already suggest a positive association between turnover rate and net diversification in some clades (e.g., fishes and flowering plants), even after accounting for ecological opportunity (Palmer et al. 2019, El Taher et al. 2021). Recent work in willows reveals rapid sex chromosome turnover coinciding with reduced introgression and lineage divergence (see Xue et al. 2024). By altering which genes are sex-linked, turnover also modulates the targets of sexual selection, redirecting inheritance of traits involved in mate choice, signaling, and parental care, and thereby influencing how new species form.

The evolutionary consequences of turnover may extend beyond reproductive isolation and diversification. Because environmental factors can alter sex determination in some taxa, changes in sex-determining architecture may interact with ecological change and population persistence. These broader conservation and management implications are discussed below.

Evolutionary and conservation consequences of inheritance restructuring

By altering how genes are inherited, turnover cycles influence not only the tempo of speciation but also the ecological and evolutionary flexibility of lineages. Genomic frameworks for biodiversity resilience emphasize the need to integrate evolving inheritance architectures into monitoring (see Buzan et al. 2025). When sex chromosome architectures reset, they reshape the recombination landscape, effective population size, and linkage of adaptive loci. These effects scale upward, from individual fitness to ecosystem dynamics, linking genomic conflict to biodiversity resilience.

Adaptive and behavioral consequences

Because sex chromosomes often contain genes involved in sensory, endocrine, and behavioral pathways, turnover may alter the inheritance context of traits involved in mate choice, signaling, and parental care. By changing which loci are sex-linked, turnover can reshape the selective environment acting on sexually selected traits and alter how reproductive isolation evolves. Comparative systems such as darters, cichlids, and frogs provide promising opportunities to test these links directly.

Conservation and global change

Recognizing sex chromosome turnover as a dynamic trait may have practical implications for conservation and management. Climate-driven sex reversal in ectotherms can generate *de facto* turnover, altering sex-determining mechanisms and destabilizing population sex ratios (Holleley et al. 2015, Bókony et al 2017). Such shifts can reduce effective population size (N_e), alter sex ratios, and influence population dynamics under environmental change (Wedekind 2017, Schwanz & Georges 2021). Because sex-determining regions (SDRs) can change identity, location, and linkage relationships on ecological timescales, management plans may benefit from treating sex-system identity as dynamic rather than fixed. Genomic monitoring of SDR location, age, and turnover frequency may improve predictions of population responses to environmental change.

Artificial translocations and captive breeding programs provide one practical example. In zebrafish, wild populations retain a localized WZ/ZZ sex-determining region that appears to have been lost or modified in standard domesticated laboratory strains (Wilson et al. 2014), illustrating how demographic history and captive propagation can reshape sex-determining architecture. More broadly, artificial translocations and captive breeding programs must also consider mitonuclear compatibility, as mismatches between mitochondrial haplotypes and local nuclear backgrounds can depress fitness and contribute to reproductive incompatibilities (Burton & Barreto 2012), and recent conservation frameworks increasingly recognize mitochondrial variation as a management-relevant axis of adaptive potential (Iverson 2024). In practice, this means that managers choosing source populations for translocation or designing captive crosses may benefit from screening both mitochondrial haplotypes and sex-determining region identity before pairing individuals, particularly in taxa with labile sex chromosomes. Because sex-determining regions can capture nuclear-encoded mitochondrial genes and alter their inheritance, moving individuals across divergent sex-system backgrounds could inadvertently generate cryptic mitonuclear mismatches, reduced fertility, biased sex ratios, or lowered offspring viability. Integrating mitochondrial and sex-chromosome architecture into breeding design may therefore reduce hidden incompatibility load and improve long-term translocation success.

Testing the escape-hatch hypothesis across scales

The mechanistic diversity of sex chromosome turnover reflects multiple evolutionary drivers that alternately amplify or relieve mitonuclear conflict. Turnovers can arise from sexually antagonistic selection, mutation load in nonrecombining regions, heterochiasmy, sex reversal, chromosomal fusion, or polyploidy, each restructuring how nuclear and cytoplasmic genomes are linked and inherited (**2**). Identifying which mechanisms dominate in different clades provides testable predictions for the intensity, sex bias, and persistence of conflict cycles.

With the growing availability of chromosome-scale assemblies, population resequencing, and hybrid-zone datasets, it is now possible to move beyond qualitative models and empirically test these predictions through mito-aware comparative genomics, functional experiments, and macroevolutionary synthesis (**Table 4**).

Table 4. Diagnostic genomic and phenotypic signatures of entrapment versus relief phases under the escape-hatch model. Unlike Table 3, which contrasts alternative mechanisms of sex-biased hybrid dysfunction, this table focuses on temporal predictions within the escape-hatch framework itself. Entrapment is predicted to be associated with sex-biased sterility, mtDNA-associated clines, and elevated rates of molecular evolution in N-mt loci, whereas relief following turnover or recombination restoration should relax these signatures and restore greater independence between nuclear and cytoplasmic evolutionary trajectories. Because individual signatures are not unique, strongest inference comes from concordance across multiple independent lines of evidence.

Signature	Entrapment phase	Relief phase	Example test
Sex-biased hybrid sterility	More likely	Less likely	Reciprocal crosses, fertility assays
Ancestry cline steepness near SDR	Steep and mtDNA-associated	Relaxed or decoupled	Mito-aware genomic clines
dN/dS of N-mt loci	Elevated or asymmetric	Reduced or redistributed	Phylogenetic dN/dS tests
Mitonuclear genotype-dependent fitness	Strong	Reduced	Reciprocal mtDNA × nuclear background assays
Segregation distortion near SDR	More likely	Reduced	Transmission ratio distortion scans
SDR coverage difference	Elevated sex-differentiated coverage	Reduced sex-differentiated coverage	Sex-differentiated coverage scans

Comparative genomics

High-quality chromosome assemblies allow every nuclear-encoded mitochondrial (N-mt) gene to be placed in its physical context relative to the sex-determining region (SDR). Comparative datasets across related taxa can date when each SDR arose, when recombination suppression expanded, and whether N-mt genes were repeatedly captured or released during turnover (Wright et al. 2017, Palmer et al. 2019, Vicoso 2019).

Different tools apply at different strata ages: in young regions, search for sex-biased heterozygosity, coverage shifts, and peaks in sex-differentiated Fst; in older strata, gene-tree monophyly and topology

weighting reveal ancient nonrecombining blocks (Bachtrog 2013, Charlesworth 2017, Darolti et al. 2019). Hybrid zones add a powerful population-level test: *mito-aware genomic clines* treat mtDNA ancestry as a covariate to identify sex-linked N-mt loci showing steeper, mtDNA-coincident barriers than neutral loci (Gompert & Buerkle 2011, Li et al. 2022, Heidbreder et al. 2025). Combining ABBA-BABA, local-ancestry barrier scans, and expression assays can reveal selection acting on mitonuclear combinations (Radcliffe et al. 2025). Diagnostic genomic and phenotypic patterns distinguishing entrapment from relief phases are summarized in **Table 4.** These signatures are *not* unique to mitonuclear entrapment; comparable patterns can arise from autosomal Dobzhansky-Muller incompatibilities, ecological selection, demographic structure, or endosymbiont-mediated distortions.

Distinguishing a localized mitonuclear barrier caused by entrapment from alternative mechanisms of hybrid dysfunction (**Table 3),** including genome-wide maternal sweeps, autosomal DMIs, and demographic structure, requires integrating multiple diagnostics and seeking convergent evidence across genomic and physiological signatures (**Table 4).** Recent simulations and theoretical work (Irwin 2025) indicate that W-drive (i.e., a genome-wide maternal sweep driven by a W-linked meiotic-drive allele) can rapidly displace mitochondrial haplotypes across hybrid zones even in the absence of strong mitonuclear incompatibilities. Spatially, entrapment produces localized barriers near the SDR, whereas W-drive produces genome-wide displacement of the mitochondrial cline (**Fig. 3**). Temporally, a W-driven sweep is expected to leave a step-like contraction in Bayesian skyline plots of mtDNA diversity that reflects a recent selective sweep of one haplotype. Additional evidence can come from sex-ratio distortions through time, distinctive W-linked centromere features, and screens for endosymbionts that sometimes mediate female-biased transmission distortions (Irwin 2025). Distinguishing localized entrapment from genome-wide maternal sweeps or demographic artifacts will ultimately require simulation-based calibration. Power and false-discovery rates for the composite **Table 4** signatures have not yet been benchmarked, and future work should quantify their sensitivity and specificity across realistic demographic and recombination parameters.

Functional and physiological validation

Functional assays provide the crucial causal bridge between genomic signatures and organismal fitness. Transcriptomic approaches can reveal whether N-mt loci within sex-linked strata show altered or sex-biased expression, incomplete dosage compensation, or disrupted coordination with mtDNA-encoded OXPHOS genes. Physiological assays, including measurements of mitochondrial respiration rate, ATP output, and oxidative stress, can then test whether these transcriptional changes translate into energetic

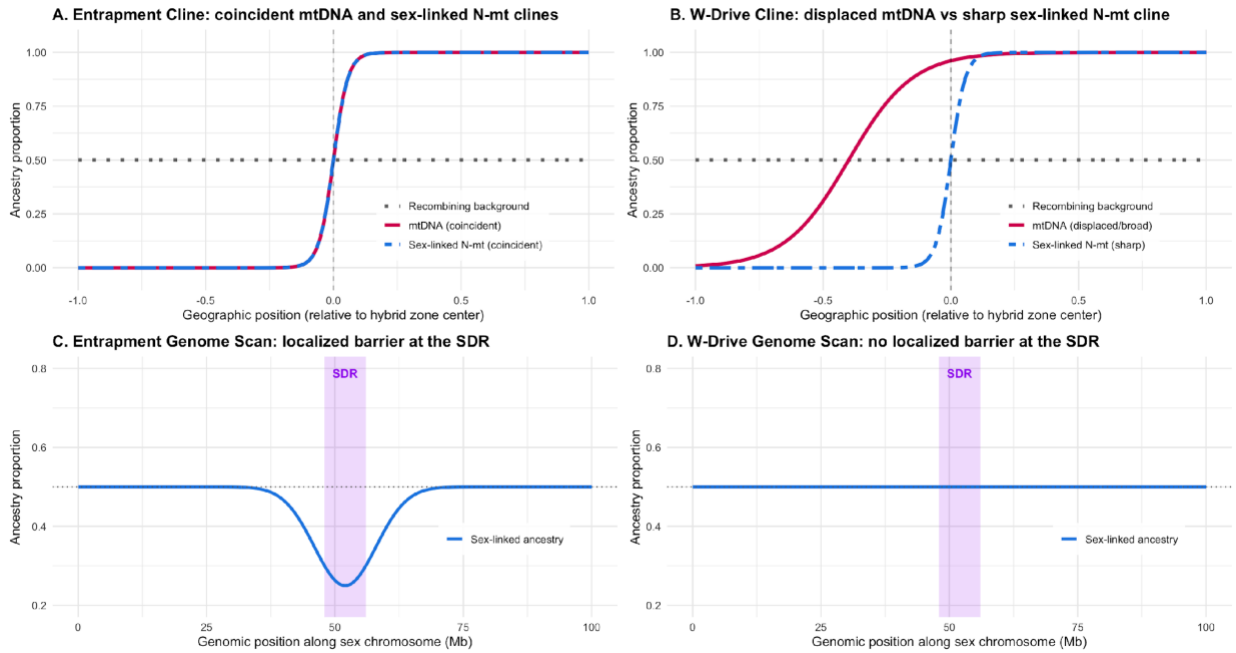
deficits (Hill 2019, Mossman et al. 2019, Moran et al. 2024). Reciprocal hybrid crosses between lineages differing in SDR identity or turnover history can determine whether hybrid dysfunction aligns with predicted entrapment or relief phases. Emerging genome-editing tools (e.g., CRISPR-mediated relocation of N-mt genes or engineered recombination windows) now make it possible to manipulate linkage explicitly, providing the first direct tests of causality. Linking differential expression, mitochondrial physiology, and fitness across turnover states will decisively establish whether mitonuclear entrapment is a primary driver of sex-biased hybrid breakdown.

Macro-evolutionary synthesis

At the broadest scale, dated phylogenies enable tests linking turnover rate, hybrid-zone width, and diversification. If turnover periodically resets recombination, then diversification should correlate with turnover frequency after controlling for ecology, life history, and range size (Palmer et al. 2019, El Taher et al. 2021). Environmental factors such as temperature or latitude can further modulate turnover, predicting clade-specific differences in the tempo of conflict and speciation.

Integration across biological scales

The escape-hatch framework unites molecular, population, and macroevolutionary perspectives. At the *molecular level*, conflict arises from mispaired OXPHOS subunits. At the *population level*, it manifests as sex-biased hybrid dysfunction and segregation distortion. At the *macroevolutionary level*, repeated turnover reshapes diversification rates. Together, these processes illustrate how *inheritance restructuring* links cellular conflict to global biodiversity patterns.



606

607 **Figure 3. Hybrid-zone and genome-scan signatures distinguishing sex-linked mitonuclear**
608 **entrapment from W-driven mitochondrial sweeps.**
609 (A) Entrapment cline: In a hybrid zone, a nuclear-encoded mitochondrial (N-mt) locus captured in a
610 newly non-recombining sex-linked stratum shows a steep ancestry cline that coincides with the
611 mitochondrial cline at the hybrid-zone center, reflecting mito-aware selection against mismatched
612 combinations. Recombining background loci remain near-neutral (have mean ancestry ~0.5). (B) W-drive
613 cline: A W-driven sweep moves the mitochondrial ancestry far across the contact zone, capturing much of
614 the range of the other species. As a result, the mtDNA cline no longer sits at the center of the zone (x =
615 0); it becomes shifted (displaced) toward one side and broadened, because the sweep acts genome-wide
616 on mitochondria, not just locally at the sex-linked stratum. The positional and width mismatch between
617 mtDNA and the sex-linked N-mt cline are indicative of a maternal sweep rather than local entrapment.
618 (C) Entrapment genome scan: Along the sex chromosome, introgression is near-neutral (~0.5 ancestry
619 proportion) in recombining regions but shows a localized dip at the sex-determining region (SDR), a
620 persistent "genomic scar'' where the N-mt locus was entrapped. (D) W-drive genome scan: Introgression
621 along the sex chromosome remains flat (mean ancestry ~0.5) across both recombining and SDR regions
622 because a W-linked sweep is predicted to displace mitochondrial haplotypes genome-wide rather than
623 creating a local incompatibility. Accordingly, no localized barrier appears at the SDR.

624

625 *Empirical support across systems*

626 Current empirical support for the escape-hatch framework remains uneven across taxa. Some systems
627 now integrate multiple independent lines of evidence, including dated sex-determining region turnover,
628 mitochondrial-haplotype-associated ancestry distortions, and measurable hybrid fitness effects, whereas

others provide only partial or indirect support. To distinguish these levels of inference, **Table 5** summarizes representative systems and grades the current strength of evidence for turnover-associated cytonuclear effects. This comparison highlights both the strongest existing case studies and a major gap in the field: relatively few systems currently combine genomic, phylogenetic, and functional assays sufficient to test the full capture–entrapment–relief cycle.

Table 5. Strength of empirical support for turnover-mediated cytonuclear entrapment across representative systems. Representative systems are graded according to the current strength of evidence supporting different components of the proposed escape-hatch framework. Columns summarize evidence for (i) documented sex chromosome turnover or restructuring, (ii) cytonuclear associations consistent with mitonuclear entrapment, (iii) hybrid dysfunction or reproductive isolation compatible with the proposed mechanism, and (iv) functional evidence linking mitochondrial genotype or OXPHOS performance to fitness. Overall support reflects qualitative integration across these categories rather than a formal quantitative score. These classifications are intended as a heuristic synthesis of the current literature and identify systems where critical components of the framework have been demonstrated versus those requiring additional empirical validation.

System	Turnover evidence	Cytonuclear association	Hybrid dysfunction	Functional evidence	Overall support	Key Citations
Darters/Percidae	strong	strong	strong	moderate	strong	Kuhl et al. 2024; Radcliffe et al. 2025
Ranid frogs	strong	suggestive	suggestive	moderate	moderate	Jeffries et al. 2018; Dufresnes & Crochet 2022; Hermaniuk et al. 2025
African cichlids	strong	suggestive	moderate	weak	moderate	El Taher et al. 2021; Gammerdinger & Kocher 2018
Willows	strong	moderate	suggestive	weak	moderate	Pucholt et al. 2017; Sanderson et al. 2021; Xue et al. 2024
Lepidoptera (mixed stability/turnover)	moderate	moderate	moderate	moderate	moderate	Fraïsse et al. 2017; Dalíková et al. 2017; Rosser et al. 2022
Armadillidium/ Wolbachia	turnover-like	strong	strong	indirect	moderate	Rigaud et al. 1997; Cordaux et al. 2011

Broadening the escape-hatch framework beyond vertebrates

Plants

In gynodioecious angiosperms, mitochondrial mutations causing cytoplasmic male sterility (CMS) select for nuclear restorer (Rf) genes, establishing a well-studied form of cytonuclear conflict that is mechanistically distinct from sex chromosome turnover (Touzet & Meyer 2014, McCauley et al. 2000). Separately, dioecy and sex-determining systems have evolved repeatedly across angiosperms, including in *Salix*, dioecious *Silene* (section *Otites*), and *Fragaria* (Renner 2014, Muyle et al. 2017, Balounova et al. 2019, Sanderson et al. 2021). Some of these lineages exhibit documented shifts in heterogamety or sex-determining architecture, whereas others retain lineage-specific sex chromosome systems once established. Together, these systems illustrate repeated evolution and diversification of plant sex-determining mechanisms, providing comparative opportunities to test whether cytonuclear interactions influence sex chromosome evolution without implying mechanistic equivalence to the vertebrate escape-hatch framework.

Insects and other invertebrates

Turnover and mitonuclear dynamics are pervasive in arthropods. Across Lepidoptera (ZW), sex chromosome–autosome fusions are documented, including a neo-W formed by W–autosome fusion in *Heliconius* (Smith et al. 2016, Rueda-M 2024), and female-biased hybrid sterility consistent with Haldane's rule is well supported (Rosser et al. 2022; but see Smith et al. 2016). In parallel, maternally inherited endosymbionts can drive mtDNA selective sweeps, generating mito–nuclear discordance in several butterfly lineages (Hurst & Jiggins 2005). *Hymenoptera* (haplodiploidy) present a distinct inheritance architecture, as males transmit only nuclear DNA (Blackmon et al. 2015), yet parasitic wasps reveal mito-conditioned hybrid fitness effects (Niehuis et al. 2008). *Drosophila* repeatedly shows large-X effects; mito-aware mapping in *D. yakuba–D. santomea* and *D. simulans–D. mauritiana* indicates X-linked N-mt compensation during early divergence (Rogell et al. 2014, Ågren et al. 2020).

Mollusks and doubly uniparental inheritance (DUI)

Several bivalves transmit distinct male and female mitochondrial lineages, termed doubly uniparental inheritance (DUI; Breton et al. 2007). Nuclear loci modulating mitochondrial segregation often show sex-biased or sex-linked expression (Kenchington et al. 2020), and hybrid zones in *Mytilus* display alternating mito–nuclear discordance with contact history (Stuckas et al. 2009). Though not classical XY/ZW

turnover, DUI demonstrates how shifts in cytoplasmic–nuclear transmission modulate conflict intensity, functionally analogous to escape and entrapment.

Fungi and protists

In fungi (e.g., *Neurospora*), large non-recombining mating-type chromosomes show introgression dynamics that hint at genomic conflict and linkage reshaping (Sun et al. 2012, Meunier et al. 2022). In algae such as *Chlamydomonas*, nuclear–organelle gene families show rapid evolution and tight coordination, indicating that shifts in cytoplasmic–nuclear transmission may modulate genomic conflict even outside classic sex chromosome systems (Craig et al. 2021)

Outlook

Sex-chromosome turnover reframes long-standing patterns of postzygotic isolation as the moving outcome of inheritance architecture rather than fixed "rules." The escape-hatch model makes this explicit: conflict intensifies when N-mt loci are entrapped in young, non-recombining strata and relaxes when turnover restores recombination or relocates the SDR. What varies among clades is not whether conflict exists, but where it sits in the genome, which sex bears the cost, and how long it persists. That variability is predictable from turnover history, SDR age, and the direction of cytoplasmic co-transmission (XY vs ZW).

In the coming years, improved chromosome-scale assemblies and long-read W/Y reconstructions will let us place every N-mt gene relative to the SDR, date strata, and test for repeated capture/release (**Table 2**). Mito-aware hybrid-zone toolkits, including genomic clines with mt ancestry as a covariate, local ancestry barrier scans, and topology-weighting, tie these histories to contemporary selection (**Table 4**; **Figs. 2,3**). Physiological assays (OXPHOS rate, ATP output) and single-cell expression will close the loop from genotype to fitness, while targeted crosses among lineages differing only in SDR identity can isolate turnover's causal role. Where feasible, manipulative tests (e.g., gene relocation or engineered recombination windows) can provide decisive falsification of entrapment predictions. Doing so will reveal whether the genomic architecture of speciation is predictable from the dynamics of inheritance asymmetry and conflict resolution. Key next steps are outlined in **Box 1**, which highlights falsifiable predictions spanning molecular to macroevolutionary scales, from decay of the large X/Z effect with SDR age to environment-coupled turnover and diversification.

A broader synthesis will come from bringing plants, invertebrates, and endosymbiont-mediated systems under the same umbrella. CMS-Rf cycles in angiosperms, DUI in bivalves, and Wolbachia-driven distortions in arthropods offer natural experiments in cyto-nuclear co-transmission. Comparing these to vertebrate XY/ZW clades will reveal whether conflict pulses follow shared rules whenever inheritance paths are rewired, irrespective of whether the mechanism is an SDR shift, recombination restoration, or cytoplasmic drive.

Finally, the escape-hatch framework has tangible value for biodiversity conservation. Climate-linked sex reversal and shifting SDRs can change demographic trajectories on management timescales. "Mito-aware" conservation - jointly monitoring mt haplotypes, SDR location/age, and sex ratios - can anticipate cryptic load, guide translocations, and reduce avoidable fitness costs in captive breeding. Because entrapment leaves localized genomic scars while W-linked sweeps displace mitochondria genome-wide, these diagnostics offer early-warning indicators before viability declines are evident (**Table 4**; **Fig. 3**). Together, these paths make the escape-hatch framework not only conceptually unifying but empirically tractable (see **Box 1**). The current diagnostics provide qualitative expectations and a framework for

Box 1. Outstanding questions and falsifiable predictions.

Molecular and population scales

1. *Clock of conflict.* Does the large X/Z effect decay with SDR age within clades, as predicted by turnover relief?
2. *Direction flips.* In lineages with XY↔ZW switches, does the sex bias of hybrid breakdown invert across sister taxa?
3. *Pathway reuse vs gene reuse.* Are convergent conflicts driven by shared OXPHOS pathways rather than identical genes?

Ecological and environmental scales

4. *Environment coupling.* Do thermal regimes that favor sex reversal increase turnover frequency?
5. *Predictive conservation.* Can early detection of SDR shifts improve population viability forecasts under climate change?

Macro-evolutionary scales

6. *Turnover–diversification correlation.* Does net diversification scale with turnover rate across taxa after controlling for ecology?
7. *Epigenetic resets.* Do methylation or small-RNA mechanisms mediate recombination restoration after turnover?

hypothesis testing; quantitative calibration via forward simulations and controlled hybrid-zone benchmarks will be essential to estimate error rates, establish thresholds, and generalize across taxa.

Conclusions

Viewed through inheritance architecture, the genome is not a static blueprint but a self-modifying system. Each sex chromosome turnover rewrites the rules that tie nuclear alleles to a single cytoplasmic lineage, sometimes amplifying conflict (entrapment), sometimes dissolving it (relief). This cycle predicts when and where hybrid dysfunction will concentrate, how its sex bias will flip across XY↔ZW transitions, and why the large X/Z effect is strong in entrenched systems yet weak or transient in labile clades. It also explains how genomic "resets" can release standing variation and open new adaptive paths, helping to connect microevolutionary coadaptation to macroevolutionary diversification. The agenda is clear: place N-mt genes on chromosome-scale maps relative to dated SDRs; test for localized, mt-coincident barriers in hybrid zones; measure energetic performance in reciprocal hybrids; and distinguish entrapment from maternal sweeps using spatial and temporal diagnostics. Extending the same logic to plant CMS–Rf cycles, DUI in mollusks, and symbiont-mediated sex-ratio distortions will reveal whether common rules govern conflict resolution whenever co-transmission changes. By treating sex chromosome turnover as both symptom and engine of mitonuclear evolution, we gain a predictive handle on how genomic architecture shapes the origin of species and the resilience of biodiversity.

Acknowledgements

Thanks to K. Delmore, T. Price, D. Kim, T. Black-Bergrud, W. Radcliffe, and A. Dongre for providing helpful discussion and feedback on this manuscript. Funding to support this work was provided by NSF IOS #2619530.

References

Ågren, J. A., Munasinghe, M., & Clark, A. G. (2020). Mitochondrial-Y chromosome epistasis in Drosophila melanogaster. Proceedings of the Royal Society B, 287(1937), 20200469.

Allendorf, F. W., & Thorgaard, G. H. (1984). Tetraploidy and the evolution of salmonid fishes. In *Evolutionary genetics of fishes* (pp. 1-53). Boston, MA: Springer US.

749 Bachtrog, D. (2013). Y-chromosome evolution: emerging insights into processes of Y-chromosome
750 degeneration. *Nature Reviews Genetics*, *14*(2), 113-124.
751 Bachtrog, D., Mank, J. E., Peichel, C. L., Kirkpatrick, M., Otto, S. P., Ashman, T. L., ... & Tree of Sex
752 Consortium. (2014). Sex determination: why so many ways of doing it?. *PLoS biology*, 12(7),
753 e1001899.
754 Ballard, J. W. O., & Pichaud, N. (2014). Mitochondrial DNA: more than an evolutionary
755 bystander. *Functional Ecology*, *28*(1), 218-231.Blaser, O., Neuenschwander, S., & Perrin, N. (2014).
756 Sex chromosome turnovers: the hot-potato model. *The American Naturalist*, *183*(1), 140-146.
757 Balounova, V., Gogela, R., Cegan, R., Cangren, P., Zluvova, J., Safar, J., Kovacova, V., Bergero, R.,
758 Hobza, R., Vyskot, B. & Oxelman, B. (2019). Evolution of sex determination and heterogamety
759 changes in section *Otites* of the genus *Silene*. *Scientific reports*, *9*(1), 1045.
760 Barton, N. H., & Charlesworth, B. (1998). Why sex and recombination?. Science, 281(5385), 1986-1990.
761 Bergero, R., & Charlesworth, D. (2011). Preservation of the Y transcriptome in a 10-million-year-old
762 plant sex chromosome system. *Current biology*, *21*(17), 1470-1474.
763 Blackmon, H., & Demuth, J. P. (2014). Estimating tempo and mode of Y chromosome turnover:
764 explaining Y chromosome loss with the fragile Y hypothesis. Genetics, 197(2), 561-572.
765 Blackmon, H., Hardy, N. B., & Ross, L. (2015). The evolutionary dynamics of haplodiploidy: genome
766 architecture and haploid viability. *Evolution*, *69*(11), 2971-2978.
767 Blackmon, H., Ross, L., & Bachtrog, D. (2017). Sex determination, sex chromosomes, and karyotype
768 evolution in insects. Journal of Heredity, 108(1), 78-93.
769 Blaser, O., Neuenschwander, S., & Perrin, N. (2014). Sex chromosome turnovers: the hot-potato
770 model. *The American Naturalist*, *183*(1), 140-146.
771 Bókony, V., Kövér, S., Nemesházi, E., Liker, A., & Székely, T. (2017). Climate-driven shifts in adult sex
772 ratios via sex reversals: the type of sex determination matters. *Philosophical Transactions of the*
773 *Royal Society B: Biological Sciences*, *372*(1729), 20160325.
774 Bouchon, D., Rigaud, T., & Juchault, P. (1998). Evidence for widespread Wolbachia infection in isopod
775 crustaceans: molecular identification and host feminization. *Proceedings of the Royal Society of*
776 *London. Series B: Biological Sciences*, *265*(1401), 1081-1090.
777 Brakefield, P. M. (2006). Evo-devo and constraints on selection. *Trends in Ecology & Evolution*, 21(7),
778 362-368.
779 Breton, S., Beaupre, H. D., Stewart, D. T., Hoeh, W. R., & Blier, P. U. (2007). The unusual system of
780 doubly uniparental inheritance of mtDNA: isn't one enough?. *Trends in genetics*, *23*(9), 465-474.
781 Bull, J. *Evolution of sex determining mechanisms*. 1983.

Burton, R. S., Ellison, C. K., & Harrison, J. S. (2006). The sorry state of F2 hybrids: consequences of rapid mitochondrial DNA evolution in allopatric populations. *The American Naturalist*, *168*(S6), S14-S24.

Burton, R. S., & Barreto, F. S. (2012). A disproportionate role for mt DNA in Dobzhansky–Muller incompatibilities?. *Molecular ecology*, *21*(20), 4942-4957.

Burton, R. S. (2022). The role of mitonuclear incompatibilities in allopatric speciation. *Cellular and Molecular Life Sciences*, 79(2), 103.

Buzan, E., de Guttry, C., Bortoluzzi, C., Street, N. R., Lucek, K., Rosling, A., ... & Waterhouse, R. M. (2025). Biodiversity Genomics Research Practices Require Harmonising to Meet Stakeholder Needs in Conservation. *Molecular ecology*, e70001.

Charlat, S., Hornett, E. A., Fullard, J. H., Davies, N., Roderick, G. K., Wedell, N., & Hurst, G. D. (2007). Extraordinary flux in sex ratio. *Science*, *317*(5835), 214-214.

Charlesworth, B. (1991). The evolution of sex chromosomes. *Science*, *251*(4997), 1030-1033.

Charlesworth, D. (2017). Evolution of recombination rates between sex chromosomes. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *372*(1736), 20160456.

Charlesworth, D. (2019). Young sex chromosomes in plants and animals. *New Phytologist*, *224*(3), 1095-1107.

Charlesworth, B., & Wall, J. D. (1999). Inbreeding, heterozygote advantage and the evolution of neo–X and neo–Y sex chromosomes. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, *266*(1414), 51-56.

Cnaani, A., Lee, B.Y., Zilberman, N., Ozouf-Costaz, C., Hulata, G., Ron, M., D'Hont, A., Baroiller, J.F., D'Cotta, H., Penman, D.J. & Tomasino, E. (2008). Genetics of sex determination in tilapiine species. *Sexual development*, *2*(1), 43-54.

Connallon, T., Camus, M. F., Morrow, E. H., & Dowling, D. K. (2018). Coadaptation of mitochondrial and nuclear genes, and the cost of mother's curse. Proceedings of the Royal Society B: Biological Sciences, 285(1871), 20172257.

Cordaux, R., Bouchon, D., & Grève, P. (2011). The impact of endosymbionts on the evolution of host sex-determination mechanisms. *Trends in Genetics*, *27*(8), 332-341.

Coyne, J.A. & Orr, H.A. (2004). *Speciation*. Sunderland, MA: Sinauer Associates.

Coyne, J. A. (2018). "Two rules of speciation" revisited. *Molecular Ecology*, *27*(19), 3749-3752.

Craig, R. J., Hasan, A. R., Ness, R. W., & Keightley, P. D. (2021). Comparative genomics of Chlamydomonas. *The Plant Cell*, *33*(4), 1016-1041.

814 Dalíková, M., Zrzavá, M., Hladová, I., Nguyen, P., Šonský, I., Flegrová, M., ... & Marec, F. (2017). New
815 insights into the evolution of the W chromosome in Lepidoptera. *Journal of Heredity*, *108*(7), 709-
816 719.
817 Darolti, I., Wright, A. E., Sandkam, B. A., Morris, J., Bloch, N. I., Farré, M., Fuller, R.C., Bourne, G.R.,
818 Larkin, D.M., Breden, F., & Mank, J. E. (2019). Extreme heterogeneity in sex chromosome
819 differentiation and dosage compensation in livebearers. *Proceedings of the National Academy of*
820 *Sciences*, *116*(38), 19031-19036.
821 Dean, R., Zimmer, F., & Mank, J. E. (2014). The potential role of sexual conflict and sexual selection in
822 shaping the genomic distribution of mito-nuclear genes. *Genome Biology and Evolution*, *6*(5), 1096-
823 1104.
824 Del-Rio, G., Rego, M. A., Whitney, B. M., Schunck, F., Silveira, L. F., Faircloth, B. C., & Brumfield, R.
825 T. (2022). Displaced clines in an avian hybrid zone (Thamnophilidae: Rhegmatorhina) within an
826 Amazonian interfluve. *Evolution*, *76*(3), 455-475.
827 Drown, D. M., Preuss, K. M., & Wade, M. J. (2012). Evidence of a paucity of genes that interact with the
828 mitochondrion on the X in mammals. *Genome Biology and Evolution*, *4*(8), 875-880.
829 Dufaÿ, M., Champelovier, P., Käfer, J., Henry, J. P., Mousset, S., & Marais, G. A. (2014). An
830 angiosperm-wide analysis of the gynodioecy–dioecy pathway. *Annals of botany*, *114*(3), 539-548.
831 Dufresnes, C., & Crochet, P. A. (2022). Sex chromosomes as supergenes of speciation: why amphibians
832 defy the rules?. *Philosophical Transactions of the Royal Society B*, *377*(1856), 20210202.
833 El Taher, A., Ronco, F., Matschiner, M., Salzburger, W., & Böhne, A. (2021). Dynamics of sex
834 chromosome evolution in a rapid radiation of cichlid fishes. *Science Advances*, *7*(36), eabe8215.
835 Ellegren, H. (2009). Genomic evidence for a large-Z effect. *Proceedings of the Royal Society B:*
836 *Biological Sciences*, *276*(1655), 361-366.
837 Ellison, C. K., & Burton, R. S. (2008). Interpopulation hybrid breakdown maps to the mitochondrial
838 genome. *Evolution*, *62*(3), 631-638.
839 Engelstädter, J., & Hurst, G. D. (2009). The ecology and evolution of microbes that manipulate host
840 reproduction. *Annual Review of Ecology, Evolution, and Systematics*, *40*(1), 127-149.
841 Estes, S., Dietz, Z. P., Katju, V., & Bergthorsson, U. (2023). Evolutionary codependency: insights into
842 the mitonuclear interaction landscape from experimental and wild Caenorhabditis nematodes. *Current*
843 *opinion in genetics & development*, 81, 102081.
844 Evans, B. J., Gvoždík, V., Knytl, M., Cauret, C. M., Herrel, A., Greenbaum, E., ... & Measey, J. (2024).
845 Rapid sex chromosome turnover in African Clawed Frogs (Xenopus) and the origins of new sex
846 chromosomes. *Molecular Biology and Evolution*, *41*(12), msae234.

847 Fraïsse, C., Picard, M. A., & Vicoso, B. (2017). The deep conservation of the Lepidoptera Z chromosome
848 suggests a non-canonical origin of the W. *Nature communications*, *8*(1), 1486.
849 Gallach, M., Chandrasekaran, C., & Betran, E. (2010). Analyses of nuclearly encoded mitochondrial
850 genes suggest gene duplication as a mechanism for resolving intralocus sexually antagonistic conflict
851 in Drosophila. *Genome Biology and Evolution*, 2, 835–850.
852 Gamble, T., Coryell, J., Ezaz, T., Lynch, J., Scantlebury, D. P., & Zarkower, D. (2015). Restriction site-
853 associated DNA sequencing (RAD-seq) reveals an extraordinary number of transitions among gecko
854 sex-determining systems. *Molecular Biology and Evolution*, *32*(5), 1296-1309.
855 Gamble, T., Castoe, T.A., Nielsen, S.V., Banks, J.L., Card, D.C., Schield, D.R., Schuett, G.W. & Booth,
856 W. (2017). The discovery of XY sex chromosomes in a boa and python. *Current Biology*, *27*(14),
857 2148-2153.
858 Gammerdinger, W. J., & Kocher, T. D. (2018). Unusual diversity of sex chromosomes in African cichlid
859 fishes. *Genes*, *9*(10), 480.
860 Gemmell, N. J., Metcalf, V. J., & Allendorf, F. W. (2004). Mother's curse: the effect of mtDNA on
861 individual fitness and population viability. *Trends in ecology & evolution*, *19*(5), 238-244.
862 Gompert, Z., & Buerkle, C. A. (2011). Bayesian estimation of genomic clines. *Molecular*
863 *Ecology*, *20*(10), 2111-2127.
864 Graves, J. A. (2016). Did sex chromosome turnover promote divergence of the major mammal groups?
865 De novo sex chromosomes and drastic rearrangements may have posed reproductive barriers between
866 monotremes, marsupials and placental mammals. *Bioessays*, *38*(8), 734-743.
867 Greiner, S., Sobanski, J., & Bock, R. (2015). Why are most organelle genomes transmitted maternally?.
868 *Bioessays*, 37(1), 80-94.
869 Han, M. J., Luo, C., Hu, H., Lin, M., Lu, K., Shen, J., ... & Dai, F. (2024). Multiple independent origins
870 of the female W chromosome in moths and butterflies. *Science advances*, *10*(25), eadm9851.
871 Haldane, J. (1922). Sex ration and unisexual sterility in animal hybrids. *J Genet*, *12*(2), 101-109.
872 Havird, J. C., Forsythe, E. S., Williams, A. M., Werren, J. H., Dowling, D. K., & Sloan, D. B. (2019).
873 Selfish mitonuclear conflict. *Current Biology*, *29*(11), R496-R511.
874 Heidbreder, P., Poikela, N., Nouhaud, P., Puukko, T., Lohse, K., & Kulmuni, J. (2025). Genomic
875 incompatibilities are persistent barriers when speciation happens with gene flow in Formica
876 ants. *bioRxiv,* 2025-03. doi: https://doi.org/10.1101/2025.03.27.645773
877 Hermaniuk, A., Czajkowska, M., Pabijan, M., Verberk, W. C., & Czarnoleski, M. (2025). Metabolic
878 consequences of hybridization in European water frogs (Pelophylax esculentus complex). *Ecology*
879 *and Evolution*, *15*(11), e72504.
880 Hill, G. E. (2014). Sex linkage of nuclear-encoded mitochondrial genes. *Heredity*, *112*(5), 469.

Hill, G. E. (2019). *Mitonuclear ecology*. Oxford University Press.

Holleley, C. E., O'Meally, D., Sarre, S. D., Marshall Graves, J. A., Ezaz, T., Matsubara, K., ... & Georges, A. (2015). Sex reversal triggers the rapid transition from genetic to temperature-dependent sex. *Nature*, *523*(7558), 79-82.Hurst, L. (1995). Selfish genetic elements and their role in evolution: the evolution of sex and some of what that entails. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 349(1329), 321-332.

Höök, L., Vila, R., Wiklund, C., & Backström, N. (2024). Temporal dynamics of faster neo-Z evolution in butterflies. *Evolution*, *78*(9), 1554-1567.

Hurst, G. D., & Werren, J. H. (2001). The role of selfish genetic elements in eukaryotic evolution. Nature Reviews Genetics, 2(8), 597-606.

Hurst, G. D., & Jiggins, F. M. (2005). Problems with mitochondrial DNA as a marker in population, phylogeographic and phylogenetic studies: the effects of inherited symbionts. *Proceedings of the Royal Society B: Biological Sciences*, *272*(1572), 1525-1534.

Hurst, G. D., & Frost, C. L. (2015). Reproductive parasitism: maternally inherited symbionts in a biparental world. *Cold Spring Harbor perspectives in biology*, *7*(5), a017699.

Irwin, D. (2025). The Driving W Hypothesis for Low Within-Population Mitochondrial DNA Diversity and Between-Population Mitochondrial Capture. *bioRxiv*, 2025-05. doi: https://doi.org/10.1101/2025.05.31.656024

Iverson, E. N. (2024). Conservation Mitonuclear Replacement: Facilitated mitochondrial adaptation for a changing world. *Evolutionary Applications*, *17*(3), e13642.

Jeffries, D. L., Lavanchy, G., Sermier, R., Sredl, M. J., Miura, I., Borzée, A., ... & Perrin, N. (2018). A rapid rate of sex chromosome turnover and non-random transitions in true frogs. *Nature communications*, *9*(1), 4088.

Kageyama, D., Narita, S., & Watanabe, M. (2012). Insect sex determination manipulated by their endosymbionts: incidences, mechanisms and implications. *Insects*, *3*(1), 161-199.

Kenchington, E. L., MacDonald, B. W., Cogswell, A., Hamilton, L. C., & Diz, A. P. (2020). Sex-specific effects of hybridization on reproductive fitness in Mytilus. *Journal of Zoological Systematics and Evolutionary Research*, *58*(2), 581-597.

Kitano, J., Ross, J. A., Mori, S., Kume, M., Jones, F. C., Chan, Y. F., ... & Peichel, C. L. (2009). A role for a neo-sex chromosome in stickleback speciation. Nature, 461(7267), 1079-1083.

Kitano, J., & Peichel, C. L. (2012). Turnover of sex chromosomes and speciation in fishes. *Environmental biology of fishes*, *94*(3), 549-558.

Kuhl, H., Euclide, P.T., Klopp, C., Cabau, C., Zahm, M., Lopez-Roques, C., Iampietro, C., Kuchly, C., Donnadieu, C., Feron, R. & Parrinello, H. (2024). Multi-genome comparisons reveal gain-and-loss

915 evolution of anti-Mullerian hormone receptor type 2 as a candidate master sex-determining gene in
916 Percidae. *BMC biology*, *22*(1), 141.
917 Layana, L., Toups, M. A., & Vicoso, B. (2026). Causes and consequences of sex-chromosome turnovers
918 in Diptera. *Evolution Letters*, qrag003.
919 Lenormand, T. (2003). The evolution of sex dimorphism in recombination. *Genetics*, *163*(2), 811-822.
920 Li, J., Schumer, M., & Bank, C. (2022). Imbalanced segregation of recombinant haplotypes in hybrid
921 populations reveals inter-and intrachromosomal Dobzhansky-Muller incompatibilities. *PLoS*
922 *genetics*, *18*(3), e1010120.
923 Lindsley, D. L., Roote, J., & Kennison, J. A. (2013). Anent the genomics of spermatogenesis in
924 Drosophila melanogaster. PLoS One, 8(2), e55915.
925 Llopart, A. (2012). The rapid evolution of X-linked male-biased gene expression and the large-X effect in
926 *Drosophila yakuba*, *D. santomea*, and their hybrids. *Molecular Biology and Evolution*, *29*(12), 3873-
927 3886.
928 Lopez, K. A., McDiarmid, C. S., Griffith, S. C., Lovette, I. J., & Hooper, D. M. (2021). Evaluating
929 evidence of mitonuclear incompatibilities with the sex chromosomes in an avian hybrid zone.
930 *Evolution*, *75*(6), 1395-1414.
931 Lubieniecki, K. P., Lin, S., Cabana, E. I., Li, J., Lai, Y. Y., & Davidson, W. S. (2015). Genomic
932 instability of the sex-determining locus in Atlantic salmon (Salmo salar). *G3: Genes, Genomes,*
933 *Genetics*, *5*(11), 2513-2522.
934 Mank, J. E. (2012). Small but mighty: the evolutionary dynamics of W and Y sex chromosomes.
935 *Chromosome Research*, *20*(1), 21-33.
936 Mank, J. E., & Avise, J. C. (2009). Evolutionary diversity and turn-over of sex determination in teleost
937 fishes. *Sexual Development*, *3*(2-3), 60-67.
938 McCauley, D. E., Olson, M. S., Emery, S. N., & Taylor, D. R. (2000). Population structure influences sex
939 ratio evolution in a gynodioecious plant. *The American Naturalist*, *155*(6), 814-819.
940 Meunier, C., Darolti, I., Reimegård, J., Mank, J. E., & Johannesson, H. (2022). Nuclear-specific gene
941 expression in heterokaryons of the filamentous ascomycete Neurospora tetrasperma. *Proceedings of*
942 *the Royal Society B*, *289*(1980), 20220971.
943 Miura, I., Shams, F., Ohki, J. I., Tagami, M., Fujita, H., Kuwana, C., ... & Ezaz, T. (2024). Multiple
944 transitions between Y chromosome and autosome in tago's Brown frog species complex. *Genes*,
945 *15*(3), 300.
946 Moran, B. M., Payne, C. Y., Powell, D. L., Iverson, E. N., Donny, A. E., Banerjee, S. M., ... & Schumer,
947 M. (2024). A lethal mitonuclear incompatibility in complex I of natural hybrids. *Nature*, *626*(7997),
948 119-127.

Morgan, T. H. (1912). Complete linkage in the second chromosome of the male of Drosophila. *Science*, *36*(934), 719-720.

Mossman, J. A., Biancani, L. M., & Rand, D. M. (2019). Mitochondrial genomic variation drives differential nuclear gene expression in discrete regions of Drosophila gene and protein interaction networks. *BMC Genomics*, *20*(1), 691.

Muyle, A., Shearn, R., & Marais, G. A. (2017). The evolution of sex chromosomes and dosage compensation in plants. *Genome biology and evolution*, *9*(3), 627-645.

Myosho, T., Takehana, Y., Hamaguchi, S., & Sakaizumi, M. (2015). Turnover of sex chromosomes in celebensis group medaka fishes. *G3: Genes, Genomes, Genetics*, *5*(12), 2685-2691.

Niehuis, O., Judson, A. K., & Gadau, J. (2008). Cytonuclear genic incompatibilities cause increased mortality in male F2 hybrids of Nasonia giraulti and N. vitripennis. *Genetics*, *178*(1), 413-426.

Orr, H. A. (1997). Haldane's rule. *Annual Review of Ecology and Systematics*, *28*(1), 195-218.

Ottenburghs, J. (2022). Avian introgression patterns are consistent with Haldane's rule. *Journal of Heredity*, *113*(4), 363-370.

Palmer, D. H., Rogers, T. F., Dean, R., & Wright, A. E. (2019). How to identify sex chromosomes and their turnover. *Molecular ecology*, *28*(21), 4709-4724.

Payseur, B. A., Presgraves, D. C., & Filatov, D. A. (2018). Sex chromosomes and speciation. *Molecular ecology*, *27*(19), 3745.

Perrin, N. (2009). Sex reversal: a fountain of youth for sex chromosomes?. *Evolution*, *63*(12), 3043-3049.

Phillips, R. B. (2013). Evolution of the sex chromosomes in salmonid fishes. *Cytogenetic and Genome Research*, *141*(2-3), 177-185.

Presgraves, D. C. (2010). The molecular evolutionary basis of species formation. *Nature Reviews Genetics*, *11*(3), 175-180.

Princepe, D., & de Aguiar, M. A. (2024). Nuclear compensatory evolution driven by mito-nuclear incompatibilities. Proceedings of the National Academy of Sciences, 121(42), e2411672121.

Pucholt, P., Wright, A. E., Conze, L. L., Mank, J. E., & Berlin, S. (2017). Recent sex chromosome divergence despite ancient dioecy in the willow Salix viminalis. *Molecular Biology and Evolution*, *34*(8), 1991-2001.

Radcliffe, W. V., Dye, M., Kim, D., Muralidhar, P. L., & Moran, R. L. (2025). Sex chromosome turnover and mitonuclear conflict drive reproductive isolation. bioRxiv preprint. https://doi.org/10.1101/2025.08.29.673102

Radzvilavicius, A., Layh, S., Hall, M. D., Dowling, D. K., & Johnston, I. G. (2021). Sexually antagonistic evolution of mitochondrial and nuclear linkage. Journal of Evolutionary Biology, 34(5), 757-766.

Rand, D. M., Haney, R. A., & Fry, A. J. (2004). Cytonuclear coevolution: the genomics of cooperation. *Trends in ecology & evolution*, *19*(12), 645-653.

Rand, D. M., & Mossman, J. A. (2020). Mitonuclear conflict and cooperation govern the integration of genotypes, phenotypes and environments. *Philosophical Transactions of the Royal Society B*, *375*(1790), 20190188.

Renner, S. S. (2014). The relative and absolute frequencies of angiosperm sexual systems: dioecy, monoecy, gynodioecy, and an updated online database. *American Journal of botany*, *101*(10), 1588-1596.

Rice, W. R. (1996). Evolution of the Y sex chromosome in animals. *Bioscience*, *46*(5), 331-343.

Rice, W. R. (2013). Nothing in genetics makes sense except in light of genomic conflict. Annual Review of Ecology, Evolution, and Systematics, 44(1), 217-237.Beukeboom, L. W., & Perrin, N. (2014). *The evolution of sex determination*. Oxford University Press.

Rigaud, T., Juchault, P., & Mocquard, J. P. (1997). The evolution of sex determination in isopod crustaceans. *Bioessays*, *19*(5), 409-416.

Rogell, B., Dean, R., Lemos, B., & Dowling, D. K. (2014). Mito-nuclear interactions as drivers of gene movement on and off the X-chromosome. BMC genomics, 15(1), 330.

Rosser, N., Edelman, N. B., Queste, L. M., Nelson, M., Seixas, F., Dasmahapatra, K. K., & Mallet, J. (2022). Complex basis of hybrid female sterility and Haldane's rule in Heliconius butterflies: Z-linkage and epistasis. *Molecular Ecology*, *31*(3), 959-977.

Rueda-M, N., Pardo-Diaz, C., Montejo-Kovacevich, G., McMillan, W. O., Kozak, K. M., Arias, C. F., ... & Salazar, C. (2024). Genomic evidence reveals three W-autosome fusions in Heliconius butterflies. *PLoS Genetics*, *20*(7), e1011318.

Sanderson, B. J., Feng, G., Hu, N., Carlson, C. H., Smart, L. B., Keefover-Ring, K., ... & Olson, M. S. (2021). Sex determination through X–Y heterogamety in Salix nigra. *Heredity*, *126*(4), 630-639.

Sardell, J. M., Josephson, M. P., Dalziel, A. C., Peichel, C. L., & Kirkpatrick, M. (2021). Heterogeneous histories of recombination suppression on stickleback sex chromosomes. *Molecular Biology and Evolution*, *38*(10), 4403-4418.

Saunders, P. A. (2019). Sex chromosome turnovers in evolution. *eLS*, 1-8.

Saunier, A., Garcia, P., Becquet, V., Marsaud, N., Escudié, F., & Pante, E. (2014). Mitochondrial genomes of the Baltic clam Macoma balthica (Bivalvia: Tellinidae): setting the stage for studying mito-nuclear incompatibilities. *BMC Evolutionary Biology*, *14*(1), 259.

Schluter, D. (2000). The ecology of adaptive radiation. OUP Oxford.

Schwanz, L. E., & Georges, A. (2021). Sexual development and the environment: Conclusions from 40 years of theory. *Sexual Development*, *15*(1-3), 7-22.

Seehausen, O. (2006). African cichlid fish: a model system in adaptive radiation research. Proceedings of the Royal Society B: Biological Sciences, 273(1597), 1987-1998.

Smith, D. A., Gordon, I. J., Traut, W., Herren, J., Collins, S., Martins, D. J., ... & Ffrench-Constant, R. (2016). A neo-W chromosome in a tropical butterfly links colour pattern, male-killing, and speciation. *Proceedings of the Royal Society B: Biological Sciences*, *283*(1835), 20160821.

Stuckas, H., Stoof, K., Quesada, H., & Tiedemann, R. (2009). Evolutionary implications of discordant clines across the Baltic Mytilus hybrid zone (Mytilus edulis and Mytilus trossulus). *Heredity*, *103*(2), 146-156.

Sun, Y., Corcoran, P., Menkis, A., Whittle, C. A., Andersson, S. G., & Johannesson, H. (2012). Large-scale introgression shapes the evolution of the mating-type chromosomes of the filamentous ascomycete Neurospora tetrasperma. *PLoS Genetics*, *8*(7), e1002820.

Touzet, P., & Meyer, E. H. (2014). Cytoplasmic male sterility and mitochondrial metabolism in plants. *Mitochondrion*, *19*, 166-171.

Uno, Y., & Matsubara, K. (2024). Unleashing diversity through flexibility: The evolutionary journey of sex chromosomes in amphibians and reptiles. *Journal of Experimental Zoology Part A: Ecological and Integrative Physiology*, *341*(3), 230-241.

Wang, J., Tao, W., Kocher, T. D., & Wang, D. (2024). Sex chromosome turnover and biodiversity in fishes. *Journal of Genetics and Genomics*, *51*(12), 1351-1360.

Wedekind, C. (2017). Demographic and genetic consequences of disturbed sex determination. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *372*(1729), 20160326.

Wright, A. E., Darolti, I., Bloch, N. I., Oostra, V., Sandkam, B., Buechel, S. D., Kolm, N., Breden, F., Vicoso, B. & Mank, J. E. (2017). Convergent recombination suppression suggests role of sexual selection in guppy sex chromosome formation. *Nature Communications*, *8*(1), 14251.

Vicoso, B., & Bachtrog, D. (2015). Numerous transitions of sex chromosomes in Diptera. PLoS biology, 13(4), e1002078.

Vicoso, B. (2019). Molecular and evolutionary dynamics of animal sex chromosome turnover. *Nature ecology & evolution*, *3*(12), 1632-1641.

Wilson, C.A., High, S.K., McCluskey, B.M., Amores, A., Yan, Y.L., Titus, T.A., Anderson, J.L., Batzel, P., Carvan Iii, M.J., Schartl, M. and Postlethwait, J.H., (2014). Wild sex in zebrafish: loss of the natural sex determinant in domesticated strains. *Genetics*, *198*(3),1291-1308.

Xue, Z. Q., Applequist, W. L., Hörandl, E., & He, L. (2024). Sex chromosome turnover plays an important role in the maintenance of barriers to post-speciation introgression in willows. *Evolution Letters*, *8*(4), 467-477.

1050 Yano, C.F., Sember, A., Kretschmer, R., Bertollo, L.A.C., Ezaz, T., Hatanaka, T., Liehr, T., Ráb, P., Al-
1051 Rikabi, A., Viana, P.F. & Feldberg, E. (2021). Against the mainstream: Exceptional evolutionary
1052 stability of ZW sex chromosomes across the fish families Triportheidae and Gasteropelecidae
1053 (Teleostei: Characiformes). *Chromosome Research*, *29*(3), 391-416.
1054 Yoshida, K., Makino, T., Yamaguchi, K., Shigenobu, S., Hasebe, M., Kawata, M., ... & Kitano, J. (2014).
1055 Sex chromosome turnover contributes to genomic divergence between incipient stickleback
1056 species. *PLoS Genetics*, *10*(3), e1004223.