Review

Conflictual speciation: species formation via genomic conflict

Bernard Crespi[1] and Patrik Nosil[2]

[1] Department of Biological Sciences, Simon Fraser University, Burnaby, B.C. V5A 1S6, Canada
[2] Department of Animal and Plant Sciences, University of Sheffield, Sheffield S10 2TN, UK

A remarkable suite of forms of genomic conflict has recently been implicated in speciation. We propose that these diverse roles of genomic conflict in speciation processes can be unified using the concept of 'conflictual speciation'. Conflictual speciation centers on the evolution of reproductive isolation as a byproduct of antagonistic selection among genomic elements with divergent fitness interests. Intragenomic conflicts are expected to readily generate Dobzhansky–Muller incompatibilities, due to population-specific interactions between opposing elements, and thus they could be especially important in speciation. Moreover, selection from genomic conflicts should be relatively unrelenting across ecological and evolutionary time scales. We explain how intragenomic conflicts can promote, or sometimes constrain, speciation, and describe evidence relating conflicts to the evolution of reproductive isolation.

How does selection promote speciation?

Natural selection contributes to speciation by the well-studied process of ecological speciation (ES), whereby divergent ecological selective pressures drive reproductive isolation (RI) between populations occupying different environments [1,2] (Figure 1). An important alternative to ES, mutation-order speciation, involves different and incompatible alleles arising by chance, and increasing in frequency, in different populations that are subject to similar ecological selective pressures [1,3]. Both of these models of speciation involve natural selection, but the causes of selection that mediate mutation-order speciation have, until recently, remained largely unknown.

In this article, we describe emerging evidence for a central role of selection from intragenomic conflict (see Glossary) in driving mutation-order speciation. Intragenomic conflict, like ecology, is a feature of all organisms, and it also imposes strong selective pressures that can lead to divergence among populations and incompatibilities between them (Figure 1). To the extent that intragenomic conflict promotes speciation across diverse taxa, a major expansion of speciation theory and empirical work in this direction might be in order.

The idea of a role for intragenomic conflicts in speciation traces to work by McClintock [4], Cosmides and Tooby [5], and Rice [6], but has undergone a resurgence due in part to genetic studies revealing that many apparent 'speciation genes' are involved in conflictual interactions [7–10]. Our goal here is to develop a broad yet explicit conceptual framework for studying how genomic conflict is involved in speciation, under the rubric of 'conflictual speciation' (CS). Intragenomic conflict represents a subset of genomic conflicts more generally (Figure 2) and forms our focus here due to recent progress in this area and the expectation that it could be especially important for speciation.

We begin by describing intragenomic conflict and how it might promote, or, alternatively, constrain speciation. We then review the types of conflict that have thus far been shown, or posited, to mediate the evolution of reproductive isolation. Finally, we further develop predictions concerning CS, clarify how it can be distinguished from, or interacts with (Box 1), other mechanisms of speciation, and consider what future studies will best move this field forward.

What is intragenomic conflict?

We define intragenomic conflict as antagonistic interactions between DNA sequences, or their products, within an individual. The 'genome' is considered as all genetic material that is inherited. Conflict can involve elements that directly distort their own transmission rate positively, by either preferentially reaching gametes, interfering with transmission of alternative alleles, or replicating disproportionately to the rest of the genome [11]. Such direct-distorting elements should increase to fixation, unless countered by opposing selective pressures. Alternatively, selfish elements can distort their transmission by altering the organism's development or behavior. These latter forms of conflict are caused by differences, in patterns of inheritance and genetic relatedness, between different elements that comprise an individual's total genomic constitution, such as nuclear genes (inherited biparentally) compared to cytoplasmic and organelle genes (inherited only maternally or paternally). Such conflicts between genomic elements can result in dynamic equilibria, or one party reaching its optimum phenotype.

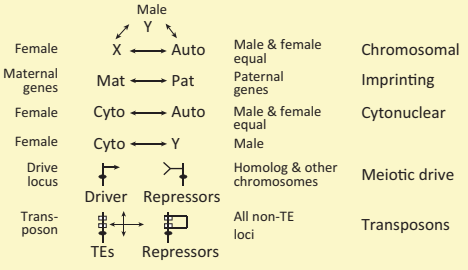
In any particular conflict, outcomes should depend primarily on the relative forms and amounts of salient phenotypic and genetic variation available for selection, and the relative intensities of selection on the elements with divergent interests. The outcome of intragenomic conflicts is alleles increasing in frequency, and often persisting, in the absence of positive effects on organism-level fitness, and normally with effects that are deleterious. As such,

Corresponding author: Crespi, B. (crespi@sfu.ca)
Keywords: speciation; intragenomic conflict; reproductive isolation; genomic conflict; post-zygotic isolation.

 0169-5347/$ – see front matter http://dx.doi.org/10.1016/j.tree.2012.08.015

Glossary

Anti-speciation gene: a gene that constrains speciation by mediating increased gene flow and reduced reproductive isolation between populations.
Conflictual speciation: a mechanism of speciation whereby genomic conflicts drive the evolution of reproductive isolation.
Cytoplasmic male sterility: sterility of male function (pollen or sperm production or viability) caused by cytoplasmically-inherited elements, often mitochondria.
Dobzhansky–Muller incompatibilities: negatively-interacting sets of genes that reduce hybrid fitness.
Ecological speciation (ES): a mechanism of speciation whereby divergent ecologically-based selection drives the evolution of reproductive isolation.
Genomic imprinting: conflict of paternally-inherited genes with maternally-inherited genes, due to their different relatedness to interacting individuals. Genes are imprinted (silenced) in either the maternal or paternal germ lines, mainly in mammals and angiosperms. Distortion occurs for phenotypes that differentially affect paternal-gene vs. maternal-gene fitness, such as investment costs imposed by offspring on the mother.
Meiotic drive: alterations to meiosis that result in unequal gamete production or survival, between autosomal heterozygotes or between different sex chromosomes. Meiotic drive may involve asymmetries in meiosis that favor one chromosome over others, or destruction of gametes that do not contain the driving allele. Drive commonly involves reduced fertility, and consequent selection on unlinked alleles to suppress the driving element.
Mutation-order speciation: a mechanism of speciation whereby reproductive isolation evolves by different, incompatible alleles arising and undergoing divergence in populations subject to similar selective pressures.
Nuclear-cytoplasmic conflict: conflict of nuclear autosomal and sex-linked genes with genes on cytoplasmic elements, such as mitochondria, chloroplasts, or symbionts. This form of conflict is due to maternal inheritance of cytoplasmic elements, compared to biparental or paternal inheritance of nuclear genes. Such inheritance differences select for cytoplasmic alleles that reduce investment in male offspring or male functions and nuclear alleles that suppress such effects, with deleterious cytonuclear interactions in hybrids.
Sex chromosome-autosome conflict: sex chromosomes are inherited and expressed in sex-dependent patterns, such that X chromosomes (in male-heterogametic species) are expected to favor female and matrilineal interests, Y chromosomes are expected to favor male and patrilineal interests, and autosomes are expected to favor both sexes equally, which means that they can favor either males (when in conflict with X chromosomes) or females (when in conflict with Y chromosomes).
Speciation gene: a gene that promotes speciation by causing a significant increase in the evolution of reproductive isolation.
Transposons: elements that replicate autonomously in genomes, and are transmitted horizontally within genomes and vertically by inheritance from parents to offspring. Replication of transposons induces genomic or chromosomal alterations that are usually deleterious, so there is selection on unlinked genes in the genome for their suppression.



speciation by intragenomic conflict contrasts strongly with other models of speciation based on adaptation in biotic interactions, although it grades into other models as a function of how intragenomic and intergenomic elements interact (Figure 2).

Intragenomic conflict commonly affects phenotypes involved in replication and reproduction, suggesting that it might represent a potent force in the evolution of reproductive isolation. Selection should also be strong for many conflictual interactions, due to the large potential gains in differential reproduction from over-replicating, winning a conflict, or pulling phenotypes towards one's preferred value. However, the actual role of intragenomic conflicts in speciation must depend on the degree to which it promotes versus constrains the evolution of reproductive isolation.

How can intragenomic conflicts contribute to speciation?

ES involves divergence between populations due to genetically-based interactions between competitors, predators and prey, hosts and parasites, or mutualists, or adaptation to different abiotic conditions. By contrast, CS by intragenomic conflict involves divergence between populations due to antagonistic interactions between opposing elements within a genome. Such interactions are expected to lead to genetic divergence, between populations, in pairs or larger sets of antagonistically-interacting loci. Intragenomic conflicts are therefore predicted to readily generate Dobzhansky–Muller incompatibilities (DMIs), a major cause of reproductive isolation. Such incompatibilities should be seen most clearly in molecular-genetic systems of DNA–protein, DNA–RNA, physiological, or developmental interaction, as have been documented for some genomic-imprinting conflicts, driver-suppressor systems, and transposon suppression (Table 1). DMIs can also involve cooperation among sets of loci with common fitness interests, in the context of conflicts against other such genomic cartels.

Intragenomic conflict is, of course, not the only process that can lead to DMIs. For example, divergent, ecologically-based selection can drive the evolution of intrinsic hybrid incompatibilities, even in the face of gene flow [12]. Intragenomic conflict should, however, be especially effective at generating DMIs for several reasons. First, genes undergoing conflict are commonly haploid (e.g., imprinted genes, sex chromosome genes, and cytoplasmic elements), or dominant in their effects, thereby engendering strong selection for favored alleles even when rare. Second, ecological selection can diminish as populations become closely adapted to their environment, whereas selection under genomic conflict can be perpetual (although sometimes rapid and episodic), due to ongoing unresolved antagonism. Finally, by virtue of acting at the genetic level itself, divergent evolution via intragenomic conflict is unlikely to be strongly dampened by phenotypic plasticity.

A possible limitation to speciation via intragenomic conflict is that intragenomic conflict does not inherently generate forms of pre-zygotic isolation such as divergent habitat preferences or sexual isolation. However, such pre-zygotic effects might evolve indirectly through the imposition of post-zygotic costs (i.e., via reinforcement-like processes) or via phenotypic effects on development or behavior (e.g., mating preferences) for some conflict elements. For example, Price and Wedell [13] describe extensive evidence that intragenomic conflict elements impose substantial costs on male fertility within populations – costs that should be exacerbated in between-population crosses. The potential for selection of pre-zygotic isolation is shown by studies of *Drosophila*, stalk-eyed flies, spider mites, and *Mus*, in which females discriminate in mating against males harboring drive elements [13,14], or hybrid-sterility inducing cytoplasmic elements such as *Wolbachia* [15,16]. By contrast, when cytoplasmic elements can

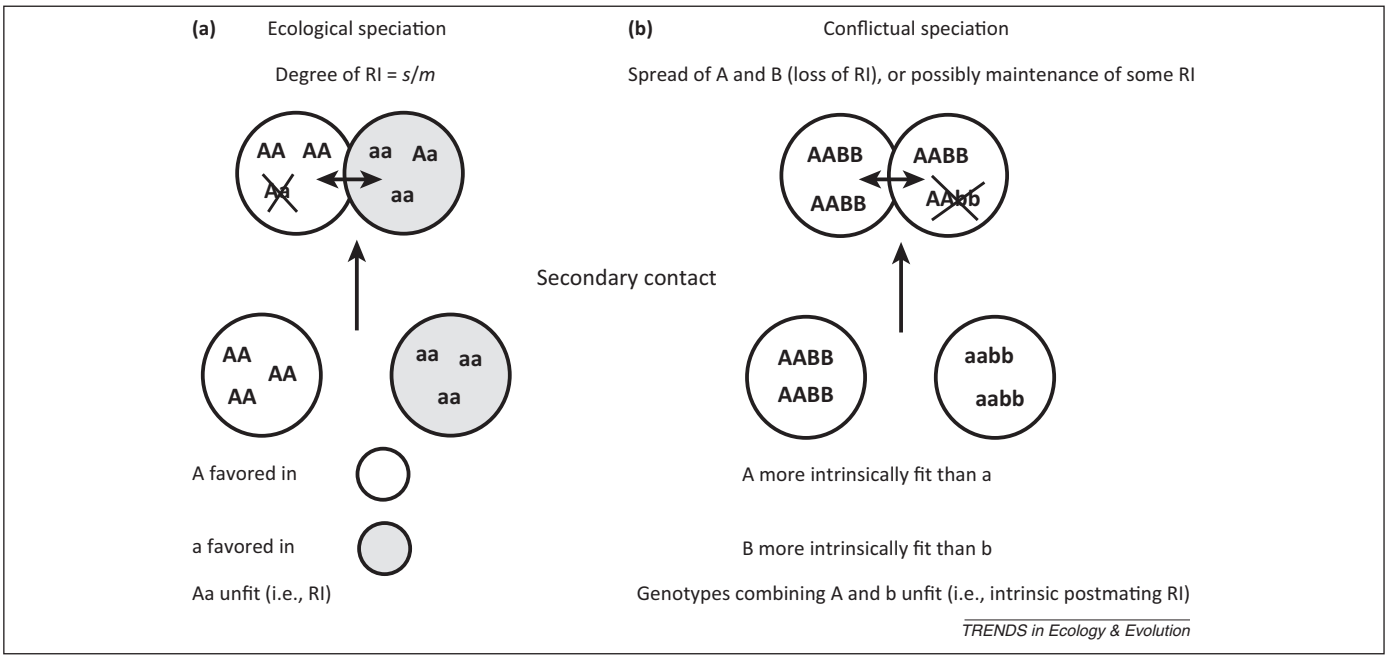


Figure 1. Ecological speciation (ES) compared to conflictual speciation. Circles represent populations and different shading represents different ecological environments. Common genotypes within each population are shown. Double-headed arrows represent gene flow. Reproductive isolation (RI), which can be imperfect (leading to gene flow) and when realized is depicted by an 'X' crossing out certain genotypes. **(a)** Under ES, populations adapt to different ecological environments via divergent selection. The resulting genetic change generates RI. In the example depicted, a single locus is considered and intermediates (i.e., heterozygotes) are unfit. However, ES could also involve epistatic interactions of the type depicted for conflictual speciation (CS). If divergence occurs with gene flow, then the degree of differentiation maintained will likely represent a balance between the strength of divergent selection (*s*) and rates of gene flow (*m*). **(b)** Under CS, intragenomic conflict creates divergence between populations. This differentiation is expected to involve multiple, epistatically interacting genes and to thus generate intrinsic postmating RI (a two locus model is shown here). If divergence occurs in the face of gene flow there can be a balance between forces that determines whether RI persists. One allele at each locus might be more fit than the other such that it can spread between both populations, eroding RI, but this will be opposed by RI itself, which is a barrier to gene flow. A secondary contact scenario is depicted here, but similar logic can be applied to primary divergence (albeit with somewhat different expected evolutionary dynamics).

successfully transmit themselves through viable hybrid matings, they are expected to favor reduced mating discrimination, as reported in *Nasonia* wasps [17]. The presence of *Wolbachia* and similar elements can also promote within-population male choice by females, as shown in *Drosophila* [18], potentially strengthening pre-mating isolation.

How can intragenomic conflicts oppose speciation?

Genomic conflict need not always promote speciation. In fact, it might sometimes oppose or constrain the process [19]. A key scenario concerns population divergence with some degree of gene flow. Suppose that two selectively and universally (in both populations) advantageous driver alleles have arisen in two different populations. The alleles

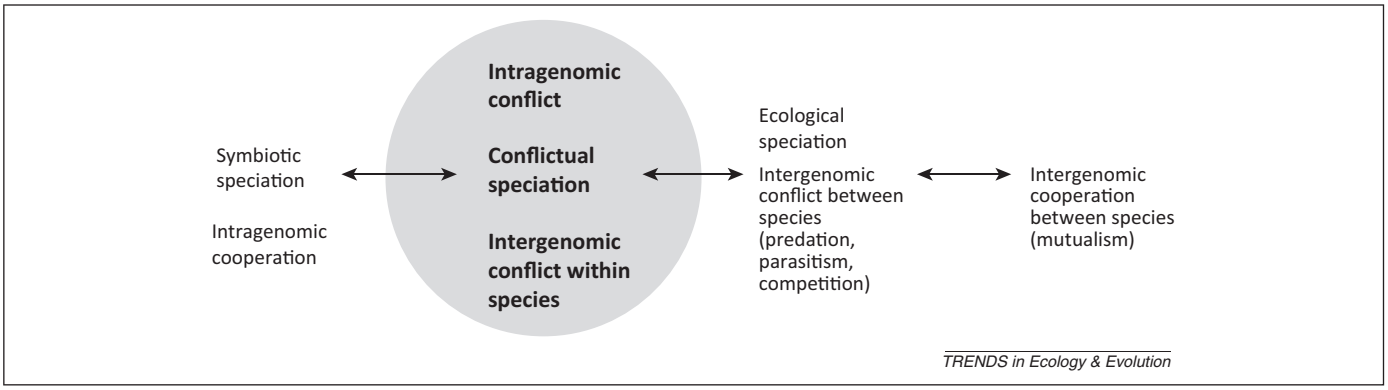


Figure 2. The relationship of conflictual speciation to other primary modes of speciation. Speciation due to genomic conflict resides along a continuum between symbiotic speciation, due to cooperation between different intragenomic elements, and ecological speciation, due to a range of interspecific interactions or adaptation to divergent abiotic conditions. Intragenomic conflict within species grades into interspecific interactions, by two criteria: whether the genomic element concerned is obligate or facultative with regard to the rest of the genome, and whether it is inherited vertically, both vertically and horizontally, or only horizontally. Autosomes, sex chromosomes, and cytoplasmic organelles are thus obligate and vertically inherited, but transposons and some endosymbionts are facultative and can be inherited vertically or via both routes. By contrast, horizontal transmission is necessarily facultative and intergenomic, usually involving parasitism, but it can evolve into vertical transmission, depending upon the selective pressures involved. Intergenomic conflicts within species include antagonistic interactions of males with females, and male gametes with female gametes. 'Conflictual speciation' is construed to include both intragenomic and intergenomic conflicts within species, but intragenomic conflicts are especially expected to readily generate Dobzhansky-Muller incompatibilities.

Box 1. Interactions between speciation models

Conflictual speciation is not mutually exclusive of other mechanisms of speciation. For example, ecological speciation via adaptation to different environments might also involve conflicting genetic elements. An interesting example concerns cytonuclear interactions in plants. Sambatti *et al.* [99] found that habitat adaptation of cytoplasmic genomes contributes to reproductive barriers in the hybridizing sunflower species, *Helianthus annuus* and *Helianthus petiolaris*. Transplant experiments were used to measure survivorship of parental genotypes, F_1 hybrids, and all possible backcross combinations of nuclear and cytoplasmic genomes in xeric and mesic habitats of the parental species. The results revealed that the cytoplasm of parental species was strongly locally adapted, with both nuclear–nuclear and cytoplasmic–nuclear interactions contributing to reduced hybrid fitness. Conflicts of maternally-inherited cytoplasmic elements with biparentally-inherited nuclear genes over investment in female function can thus be mediated by selection for cytoplasmic–nuclear cooperation. Similar considerations should apply for other ecologically-adapted cytoplasmic elements, such as some bacterial symbionts [55] and mitochondria.

Transposable elements, and imprinted genes, are regulated epigenetically, such that their expression and effects can be modulated by environmental conditions such as ecological stress [38]. Comparably, in *Drosophila*, winter temperature is strongly associated with the frequency of meiotic drive elements across North America and Canada, suggesting balances between drive and ecology [26]. Ecologically-mediated commensal bacterial flora mediate mate choice in some *Drosophila* [100], which implicates intragenomic conflict depending upon bacterial effects and modes of transmission. Finally, intragenomic conflicts might also bolster ecological speciation by adding intrinsic postmating aspects of isolation to any existing premating components. This process might be especially important for ensuring the irreversibility of speciation, particularly in the face of changing environmental conditions.

will move between populations via gene flow, and because one allele will almost always have at least a slightly higher selective advantage than others, a likely outcome is that the same, most-advantageous allele will fix in both populations [3]. Alternatively, imagine that a driver allele, a novel transposon, or a distorting cytoplasmic element, arises in one population. Under even low levels of gene flow, it could spread readily to the other population, due to its strong selective advantage and the expected initial absence of suppressing alleles in either population (Figure 1). Similar logic applies to suppressing elements, once selfish elements have spread. All of these scenarios can prevent different incompatible sets of alleles from fixing in different populations that experience gene flow, in sharp contrast to the plausibility of divergence under gene flow by divergent ecological selection [1,20]. An apparent example of higher introgression via gene flow by driving sex-chromosome elements in a *Mus* hybrid zone is described by [21]; however, in many hybrid zones, sex chromosomes show reduced introgression compared to autosomes [22,23]. The high incidence of within-population polymorphism in conflict elements suggests that gene flow need not lead to local fixation (e.g., [24–26]), but few studies have tested for among-population variation in the frequencies of conflict elements, in relation to patterns of gene flow.

These considerations suggest that unless strong barriers to hybridization are initially present, or evolve rapidly in relation to the onset and strength of gene flow, intragenomic conflict elements might sometimes actually represent 'anti-speciation genes', that effectively homogenize populations, at least for the locus or chromosome that mediates distortion. Such considerations might apply more to distorting elements with driver–suppressor dynamics (as in meiotic drive) than to tug-of-war interactions (as in genomic imprinting and X-Y-autosome interactions), although further work on this topic is required.

What empirical evidence supports the hypothesis of CS?

An especially important challenge for studies of CS, compared to ES, is that the phenotypic expression of intragenomic conflict is commonly either highly episodic, and thus difficult to capture in progress, or invisible unless perturbed by hybridization, and thus difficult to discern without experimental analyses or studies of hybrid zones [8]. Despite these limitations, a primary motivation for formalizing the hypothesis of CS has been the rapidly-expanding list of cases where reproductive isolation has been shown to be associated in some way with intragenomic conflicts (Table 1). Such work includes many of the best-understood 'speciation genes', where reproductive isolation has been linked with specific molecular-genetic mechanisms. Moreover, the broad taxonomic distribution of intragenomic-conflict effects in speciation suggests considerable generality in their impacts. We next describe the range of mechanisms that can cause CS via intragenomic conflict, and the evidence for their effects in natural populations.

Drive

Drive involves intragenomic conflicts of driver elements and linked loci versus non-driver alleles at the drive locus, as well as any loci that are unlinked to the driver and suffer reduced fitness. Such conflicts can occur during male or female meiosis, gametogenesis or gamete activity [7], during gestation [27], or between different-sex offspring of a brood [28], and they can involve autosomes or sex chromosomes (Table 1). Under meiotic drive, post-zygotic isolation appears to result from 'unleashing' of drive elements into a genetic background that lacks suppression [8], which causes incompatibilities due to dysregulated meiosis. Such impacts of drive might contribute to the disproportionately-large effect of the X chromosome in speciation, and to Haldane's rule that hybrid sterility usually affects the heterogametic sex [7]. Autosomal drive can also explain karyotypic variability between populations [29,30], given its ability to cause rapid chromosomal changes; however, karyotype changes accompanying speciation can also be caused by 'unleashed' transposon activity [31]. Centromeric drive, whereby chromosomes gain a transmission advantage in female meiosis due to allelic differences in their centromeric DNA sequence, which is countered by proteins that interact with the centromeric sequence, appears to also represent an important, general cause of reproductive isolation. Thus, this process can explain the remarkably high divergence among species in heterochromatic repeat regions that flank centromeres, karyotype difference between related species, emergence of 'neocentromeres', the evolution of new sex chromosomes, positive selection of DNA-binding proteins, and alterations to centromere configurations in hybrids [32–35]. Although a notable proportion of DMI systems involve DNA-binding proteins

Table 1. Intragenomic conflicts have been linked with speciation in a diverse array of taxa

Form of conflict	Taxa	Evidence for association with speciation	Refs
Drive	*Hordeum* (barley)	Rapidly-evolving centromeric protein mediates hybrid inviability	[79]
	Mimulus (monkeyflowers)	Female meiotic drive associated with male sterility, linked to centromeric repeats	[24]
	Oryza (rice)	Level of transmission ratio distortion positively correlated with genetic distance and pollen inviability among populations	[80]
	Zea (maize)	Knob elements mediate female drive and deleterious effects on male gametes	[81]
	Drosophilia (flies)	Links of male hybrid sterility or inviability with heterochromatic and/or DNA-binding regions	[82–87]
	Mus (mice)	t locus drive systems maps to same locus as hybrid sterility, in crosses of *Mus spretus* with *Mus domesticus*	[88]
	Rodents, humans, and other metazoans	*PRDM9* gene associated with hybrid and intraspecific sterility, mediates recombination and biased gene conversion, and undergoes rapid adaptive molecular evolution	[36,37]
Imprinting	*Arabidopsis* (thale cress)	Alterations to imprinting in hybrids associated with disrupted endosperm development, imprinted gene dosage	[45,89,90]
	Diverse angiosperms	Opposite deleterious alterations on endosperm development in hybrids	[46,48]
	Diverse angiosperms	Unlilateral imprinting effects on hybrid seed development, in self-compatible × self-incompatible crosses	[73]
	Mus (mice)	Disruption to imprinted genes in hybrids, altered growth; links to RI unknown	[91]
	Peromyscus (mice)	Reciprocal crosses show opposite alterations to placentation and growth-related phenotypes, due to imprinted-gene alterations, resulting in hybrid inviabilities	[92]
Transposons	*Arabidopsis* (thale cress)	Transposons upregulated in hybrids, associated with seed lethality	[93]
	Helianthus (sunflowers)	Three hybrid species show much higher incidence of transposons than parental species; links to RI unknown	[94]
	Oryza, Zizania (rice, wild rice)	DNA introgression associated with transposon activation; links to RI unclear	[95]
	Drosophila (flies)	Maternally inherited small RNAs interact with paternally inherited transposons, with hybrid sterility in crosses that differ in presence of particular paternal transposons; hybrid dysgenesis	[42,43]
	Macropus (kangaroos)	Hybrids show centromeric instability, associated with transposon and satellite replication; some hybrids sterile	[96]
	Mus (mice)	Epigenetic transposon silencing mechanisms disrupted in hybrids leading to placental dysfunction	[31,97]
Cytonuclear conflicts	Many angiosperms	Cytoplasmic male sterility in hybrids	[10,52,98]
	Drosophila paulistorum	In hybrids, mutualistic symbionts over-replicate, becoming deleterious	[16]
	Nasonia (wasps)	100-fold increase in *Wolbachia* loads in hybrids, and reduced fecundity	[17]
Chromosomal conflicts	*Drosophila* (flies), *Canis* (dogs), *Mus* (mice)	Epistatic interactions between X and autosomes affecting sexual phenotypes and/or hybrid fitness	[57,60,62,64]

interacting with heterochromatic repeats (such as those found at centromeres), such systems have thus far been linked with drive only for the classic *Drosophila* SD-Rsp system.

Gene conversion can also represent a form of drive involving intragenomic conflict, whereby over-replication by the 'converter' allele leads to reduced individual fitness [36,37]. Such conflict occurs most prominently during meiotic recombination. A recent model for the evolution of recombination hotspots posits that such gene conversion can drive an antagonistic coevolutionary arms race between converter genes and modifiers of gene conversion, such as the 'speciation gene' *PRDM9*, which codes for a DNA-binding protein that orchestrates recombination. This model can explain the extraordinarily rapid adaptive molecular evolution of *PRDM9*, and how it contributes to male infertility in humans and hybrids of mice and other taxa.

Transposons

Transposable elements comprise a considerable fraction of the genome in most eukaryotes. Such elements can evolve rapidly, and transposition is associated with high rates of deleterious mutation and chromosomal alterations; however, their activity is usually repressed by mechanisms such as methylation and small RNAs [38,39].

Transposons have been proposed as major drivers of speciation, based mainly on striking differences among lineages in their suites of transposable elements, their roles in causing deleterious mutations when active, the potential for these elements to mediate karyotypic reorganization, and recurrent 'domestication' of transposons to serve as adaptive contributors to genome functions [11,31,38–41]. Evidence for direct, causal roles of transposable elements in the speciation process has, until recently, been restricted mainly to studies of *Drosophila* that demonstrate production of sterile progeny from crosses that

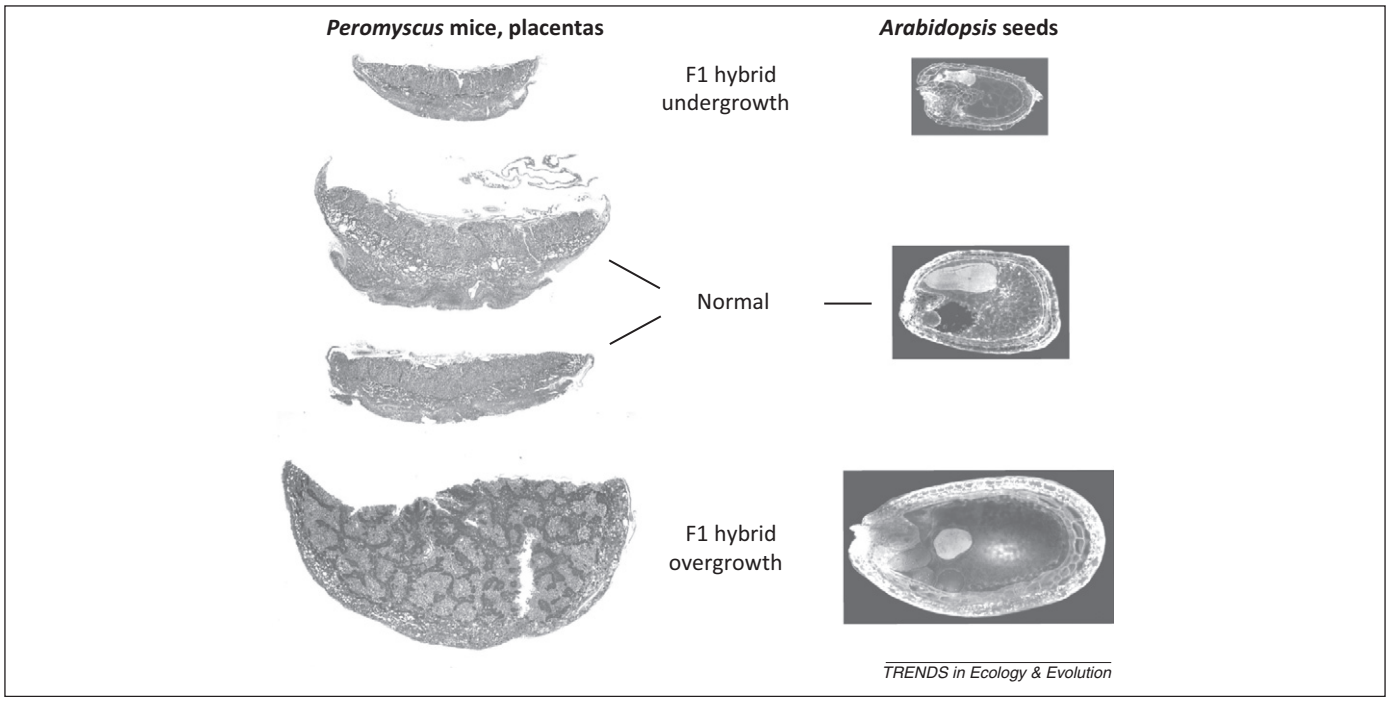


Figure 3. Parallel effects of imbalanced genomically-imprinted genes on hybrid offspring, in mammals and angiosperms. In *Peromyscus* mice, and *Arabidopsis* plants, hybrids show either overgrowth or undergrowth of placental or endosperm tissues, depending upon the direction of the cross. Such reciprocal changes are caused by alterations to dosages of imprinted genes that exert differentially-strong effects on tissues that impose demands on the mother. Hybridization in these intragenomic conflict situations results in strong post-zygotic isolation. Photographs courtesy of Paul Vrana and Rod Scott.

differ in the presence or absence of particular forms of transposons. Such 'hybrid dysgenesis' in *Drosophila* has been shown to result from incompatibilities of paternally inherited transposable elements with maternally inherited RNAs [42,43]; similar interactions now also appear to occur in *Arabidopsis* [44].

Imprinting

Genomic imprinting involves conflict of paternally-expressed with maternally-expressed genes, frequently over energetic demands imposed by developing offspring on the mother. Key features of imprinting systems, as regards reproductive isolation, include: (i) strong sensitivity to gene-dosage effects; (ii) regulation by epigenetic factors, including methylation and histone modifications; and (iii) differential effects on the tissues that impose demands: the placenta in mammals and its equivalent, endosperm tissue, among angiosperms. In hybrids of *Peromyscus*, *Mus*, *Arabidopsis*, and some other angiosperms, alterations to dosages of imprinted genes, and epigenetic dysregulation of imprinting, have been linked with abnormal development of the placenta or endosperm (Table 1). Such deleterious alterations lead to reduced hybrid viability mainly through placental and fetal, or endosperm, undergrowth (due to biases towards increased relative dosages of maternally-expressed genes), or overgrowth (due to biases towards increased paternal dosages), depending upon the direction of the cross (Figure 3). Among angiosperms, hybrid incompatibilities often manifest through alterations to endosperm growth, suggesting that dysregulated imprinted-gene dosages, due to genetic and epigenetic divergence or ploidy imbalances, represent a common mechanism for the evolution of species barriers in this group [45–48]. However, other, interacting mechanisms, such as transposon silencing via small RNAs, can also generate differential effects on hybrid seed development [44,49].

Cytonuclear conflicts

Cytonuclear incompatibilities in hybrids are caused by divergent outcomes of conflict between maternally inherited organelles or symbionts that sabotage male function (or male production) and biparentally-inherited nuclear 'restorer' genes [10,50,51]. Such incompatibilities are very common in hermaphroditic and gynodioecious (hermaphrodite plus female) plants [10,19,52]. Moreover, intracellular symbionts, which also generate hybrid cytonuclear incompatibilities, are found in most insects [9,51]. In each of these situations, post-zygotic isolation results from deleterious side effects of cytoplasmic distorter genes in hybrids [53], within which nuclear genes that maintain or restore male functions (in plants) or hybrid fitness (in animals) are absent or mismatched.

Despite the frequent documentation of cytonuclear incompatibilities, a clear role for such systems in the early stages of speciation remains to be demonstrated. Moreover, cytonuclear incompatibilities can arise not just from conflict, but also from population or species-specific interactions that are mutualistic [54,55]. Such cooperative interactions might be highly effective in driving speciation because hybridization should be deleterious for the genomes of both parties.

Chromosomal conflicts

Conflicts between autosomes, X, and Y chromosomes are expected with regard to not just sex ratios and meiotic drive effects, but also over phenotypes with differing optima between males and females for which sex-limitation does not independently optimize each sex [56]. Such conflicts are consistent with large sex-chromosome effects on

Table 2. Conflictual speciation differs from ecological speciation in a large suite of fundamental ways

Factor affecting speciation	Conflictual speciation	Ecological speciation
Natural selection	Conflict-mediated selection differs between populations due to differences in mutations or mating/social system divergence	Divergent ecological selection among populations
Response to selection	Reduced organismal adaptation due to distorting elements and increased adaptation due to their suppression	Increased population adaptation
Molecular-evolutionary divergence patterns	Recurrent positive selection on distorting elements and suppressors; involvement of rapidly-evolving repeat elements	Positive selection episodes for traits related to ecology
Gene flow	Expected to often readily homogenize populations for conflict loci	Counteracted by divergent selection
Reproductive isolation (RI)	Mainly post-zygotic	Pre- or post-zygotic
RI-related traits	RI caused mainly by traits related to reproduction	RI caused by traits related to ecology
Variation in RI between reciprocal crosses	Asymmetries expected under drive, nuclear-cytoplasmic conflict, transposon effects; imprinting effects should generate opposite extreme phenotypes	Asymmetries or opposite extremes not necessarily predicted
Genetics	Enrichment of RI loci to X, Y, centrosomes, imprinted genes, transposons, or suppression elements	Any chromosome, but perhaps accentuated divergence in regions of low recombination
Sex chromosome relative size	Larger sex chromosomes may favor divergence, or reduce it via driver gene-flow effects	Expected effect unclear
Dobzhansky–Muller incompatibilities	Should be generated 'automatically' by conflict and 'cooperation' in suppressing conflict elements	May be generated if ecological traits are affected by genes with negative epistatic effects

speciation [7], but have seldom been studied with regard to reproductive isolation. A key differentiating prediction of chromosomal conflict theory, compared to other causes of large-X effects, involves epistatic interactions, between sex chromosomes and autosomes, that affect sexually-dimorphic phenotypes [57,58], with predictable directional phenotypic alterations due to losses or gains of function by either party due to hybridization. Possible examples involve: (i) widespread overexpression of spermatogenesis-associated X-chromosomal genes in *Mus* hybrids, with male sterility apparently related to interactions of X-linked genes in one parental species with autosomal or Y-linked genes in the other [59,60]; and (ii) strong interactions between autosomes and sex chromosomes mediating male hybrid sterility in *Drosophila* [61–64].

What predictions and tests can be used to further evaluate CS?

CS and ES differ with regard to factors favoring, or disfavoring, the evolution of reproductive isolation (Table 2). These differences serve as bases for developing empirical tests of CS in relation to ES and other processes of speciation.

CS is driven by conflict at the genetic level. Thus, ideal tests of CS involve molecular-genetic information concerning the conflicting elements causing reproductive isolation. For example, a positive relationship is predicted between the degree of overall population divergence (or positively-selected divergence) in conflicting genetic elements and the degree of post-zygotic reproductive isolation. Such an association should be tempered by the fact that population divergence in conflicting elements will be affected by processes other than just the strength of conflict. CS can also be implicated by mapping of DMIs to conflict-associated genetic regions or by patterns of positively-selected divergence among populations and species in genetic elements whose basic function, usually in processes related to reproduction, remains highly conserved. Indeed, Presgraves [8] noted that most protein-coding genes known to cause DMIs, and for which evolutionary analyses have been implemented, showed patterns of recurrent, long-term positive selection.

A major limitation of tests for CS that tie the presence and strength of conflict to the degree of reproductive isolation is that different processes can result in similar patterns. For example, each of the three major 'rules' of speciation: Haldane's rule, the large X effect, and asymmetric post-mating isolation, can be driven by intragenomic conflicts or other, non-conflictual processes [65,66]. Similar considerations apply to specific processes. Centrometric drive predicts stronger genetic divergence at centromeres than at other genomic regions [67]. This same pattern could also arise from higher mutation rates and concerted evolution in such regions (and other regions with repetitive DNA, such as heterochromatin), from background selection against deleterious alleles generating more divergence by drift in regions of low recombination, or from genes involved in adaptive divergence and reproductive isolation being able to differentiate more readily when they reside in regions of low recombination [22,68,69]. Likewise, intrinsic post-zygotic isolation, if it exists, can be attributable to many processes other than CS [12,70,71]. Finally, transmission ratio distortion can be caused by mechanisms other than intragenomic conflict, including gametophyte interactions in plants [25] or post-meiotic selection.

In the absence of data allowing tests of CS at the genetic level, a number of tests incorporating phenotypic information might provide insights. One example concerns the centromeric drive hypothesis, which proposes conflict between centromeric DNA repeats and centromere-binding proteins over skewing of female meiosis. Such conflict results in an arms race between the two structural units, driving rapid coevolution (for review see [72]). If this arms race follows different trajectories in different populations, then hybrids might develop DMIs. If centromeric drive is

occurring, then an under-representation of recombinant genotypes is predicted in laboratory crosses. This prediction could be tested without detailed knowledge about the underlying conflicting genetic elements (e.g., [67]). Similarly, genomic imprinting effects are expected to increase with greater multiple paternity within populations. CS driven by genomic imprinting therefore predicts a positive relationship between the degree of multiple paternity, or population divergence in mating systems, and the strength of reproductive isolation [73].

CS also predicts associations of post-zygotic isolation phenotypes (e.g., disrupted placentation, or altered sex ratios and disrupted meiosis) with particular forms of conflict element (e.g., imprinted genes or driving sex chromosomes). Moreover, divergence in two opposite directions from normality is predicted for reciprocal-cross hybrid phenotypes affected by conflicting genetic elements that undergo tug-of-war types of interaction [56]. In some cases, specific asymmetries are expected in the phenotypes of offspring from reciprocal crosses, such as pathologically-large offspring from hybrid combinations of a 'strong' paternally-expressed imprinted element with a 'weak' maternally-expressed, interacting element, and pathologically-small offspring from the reciprocal cross [73].

Falsification steps might also be taken to address the likelihood of CS via a strong inference approach. For example, if reproductive isolation exists and one can falsify ES, then CS remains as a possibility. Such tests could be accomplished by conducting reciprocal transplant experiments using populations that are known to exhibit some reproductive isolation. If selection is absent or uniform across environments, as observed in some experiments [74,75], the hypothesis of ES is eliminated. The predictions discussed in this section are summarized in Table S1.

Conclusions and future directions

We have presented a conceptual framework for understanding and analyzing how speciation can be driven by selection due to intragenomic conflict, a process intrinsic to every organism. A rapidly-increasing body of empirical evidence supports the importance of conflictual interactions in the evolution of reproductive isolation. However, few studies have conclusively linked intragenomic conflict with reproductive isolation, probably because such conflicts are difficult to demonstrate, and speciation is challenging to study. An important consideration, even when conflict can be linked to reproductive isolation, is the timing of evolution: for conflict to be causally involved in speciation it must drive increases in reproductive isolation, and thus act before speciation is complete.

This review has highlighted several key areas for future research, to help accelerate progress in developing and testing theories of CS.

First, further theoretical modeling of conflicts in speciation is required, to establish the conditions under which different genomic conflicts are expected to promote, or constrain, the evolution of reproductive isolation (e.g., [76,77]).

Second, studies of populations at variable points in the speciation process are required to determine if intragenomic conflicts drive or follow the evolution of reproductive isolation.

Third, the genomic nature of CS compels dovetailing of detailed molecular-genetic analyses with field, mating, and comparative studies, to elucidate mechanisms of intragenomic conflict, determine how they become dysregulated in hybrids, and extrapolate to differences among species and higher taxa.

Finally, the study of CS and its mechanisms interfaces closely with several fields of applied importance, including human fertility [37], the somatic evolution of cancer [78], and improvement of major crop plants. Most generally, a comprehensive understanding of how conflictual as well as extrinsic ecological selection contribute to speciation should provide new insights into the origins of diversity at all levels, from cells to the major lineages of life.

Acknowledgments

We thank Francisco Úbeda, Steve Frank, Jeff Joy, Mikael Mökkönen, and the Simon Fraser University Fab-lab for helpful comments. We also thank Tom Price for discussions about meiotic drive, Sam Flaxman for points about the predictions of mutation-order speciation, Robert Trivers for discussions about conflict in general, and Aneil Agrawal for suggesting 'anti-speciation' effects of driving elements. P.N. is funded by the European Research Council (Starter Grant NatHisGen), and B.C. thanks NSERC for support.

Appendix A. Supplementary data

Supplementary data associated with this article can be found at http://dx.doi.org/10.1016/j.tree.2012.08.015.

References

1 Schluter, D. (2009) Evidence for ecological speciation and its alternative. *Science* 323, 737–741
2 Nosil, P. (2012) *Ecological Speciation*, Oxford University Press
3 Nosil, P. and Flaxman, S.M. (2011) Conditions for mutation-order speciation. *Proc. R. Soc. B: Biol. Sci.* 278, 399–407
4 McClintock, B. (1980) Modified gene expressions induced by transposable elements. In *Mobilization and Reassembly of Genetic Information* (Scott, W.A. *et al.*, eds), pp. 11–19, Academic Press
5 Cosmides, L.M. and Tooby, J. (1981) Cytoplasmic inheritance and intragenomic conflict. *J. Theor. Biol.* 89, 83–129
6 Rice, W.R. (1998) Intergenomic conflict, interlocus antagonistic coevolution, and the evolution of reproductive isolation. In *Endless Forms: Species and Speciation* (Howard, D.J. and Berlocher, S.H., eds), pp. 261–270, Oxford University Press
7 McDermott, S.R. and Noor, M.A.F. (2010) The role of meiotic drive in hybrid male sterility. *Philos. Trans. R. Soc. B: Biol. Sci.* 365, 1265–1272
8 Presgraves, D.C. (2010) The molecular evolutionary basis of species formation. *Nat. Rev. Genet.* 11, 175–180
9 Johnson, N.A. (2010) Hybrid incompatibility genes: remnants of a genomic battlefield? *Trends Genet.* 26, 317–325
10 Rieseberg, L.H. and Blackman, B.K. (2010) Speciation genes in plants. *Ann. Bot.* 106, 439–455
11 Burt, A. and Trivers, R. (2006) *Genes in Conflict: The Biology of Selfish Genetic Elements*, Harvard University Press
12 Agrawal, A.A. *et al.* (2011) Ecological divergence and the evolution of intrinsic postmating isolation with gene flow. *Int. J. Ecol.* 2011, 1–15
13 Price, T.A.R. and Wedell, N. (2008) Selfish genetic elements and sexual selection: their impact on male fertility. *Genetica* 132, 295–307
14 Carroll, L.S. *et al.* (2004) Fitness effects of a selfish gene (the *Mus* T complex) are revealed in an ecological context. *Evolution* 58, 1318–1328
15 Vala, F. *et al.* (2004) *Wolbachia* affects oviposition and mating behaviour of its spider mite host. *J. Evol. Biol.* 17, 692–700
16 Miller, W.J. *et al.* (2010) Infectious speciation revisited: impact of symbiont-depletion on female fitness and mating behavior of *Drosophila paulistorum*. *PLoS Pathog.* 6, e1001214
17 Chafee, M.E. *et al.* (2011) Decoupling of host-symbiont-phage coadaptations following transfer between insect species. *Genetics* 187, 203–215

18 Koukou, K. *et al.* (2006) Influence of antibiotic treatment and *Wolbachia* curing on sexual isolation among *Drosophila melanogaster* cage populations. *Evolution* 60, 87–96
19 Rieseberg, L.H. and Willis, J.H. (2007) Plant speciation. *Science* 317, 910–914
20 Price, T.D. (2007) *Speciation in Birds*, Roberts and Company
21 Macholan, M. *et al.* (2008) Genetic conflict outweighs heterogametic incompatibility in the mouse hybrid zone? *BMC Evol. Biol.* 8, 271
22 Nachman, M.W. and Payseur, B.A. (2012) Recombination rate variation and speciation: theoretical predictions and empirical results from rabbits and mice. *Philos. Trans. R. Soc. B: Biol. Sci.* 367, 409–421
23 Carneiro, M. *et al.* (2010) Speciation in the European rabbit (*Oryctolagus cuniculus*): islands of differentiation on the X chromosome and autosomes. *Evolution* 64, 3443–3460
24 Fishman, L. and Saunders, A. (2008) Centromere-associated female meiotic drive entails male fitness costs in monkeyflowers. *Science* 322, 1559–1562
25 Scopece, G. *et al.* (2010) Polymorphism of postmating reproductive isolation within plant species. *Taxon* 59, 1367–1374
26 Dyer, K.A. (2012) Local selection underlies the geographic distribution of sex-ratio drive in *Drosophila neotestacea*. *Evolution* 66, 973–984
27 Haig, D. (1996) Gestational drive and the green-bearded placenta. *Proc. Natl. Acad. Sci. U.S.A.* 93, 6547–6551
28 Rice, W.R. *et al.* (2008) Sexually antagonistic "zygotic drive" of the sex chromosomes. *PLoS Genet.* 4, e1000313
29 Fedyk, S. and Chetnicki, W. (2007) Preferential segregation of metacentric chromosomes in simple Robertsonian heterozygotes of *Sorex araneus*. *Heredity* 99, 545–552
30 Ropiquet, A. *et al.* (2008) Chromosome evolution in the subtribe Bovina (Mammalia, Bovidae): the karyotype of the Cambodian banteng (*Bos javanicus birmanicus*) suggests that Robertsonian translocations are related to interspecific hybridization. *Chromosome Res.* 16, 1107–1118
31 Brown, J.D. and O'Neill, R.J. (2010) Chromosomes, conflict, and epigenetics: chromosomal speciation revisited. In *Annual Review of Genomics and Human Genetics, Vol 11* (Chakravarti, A. and Green, E., eds), pp. 291–316
32 de Villena, F.P.M. and Sapienza, C. (2001) Female meiosis drives karyotypic evolution in mammals. *Genetics* 159, 1179–1189
33 Malik, H.S. and Henikoff, S. (2009) Major evolutionary transitions in centromere complexity. *Cell* 138, 1067–1082
34 van Doorn, G.S. and Kirkpatrick, M. (2007) Turnover of sex chromosomes induced by sexual conflict. *Nature* 449, 909–912
35 Yoshida, K. and Kitano, J. (2012) The contribution of female meiotic drive to the evolution of neo-sex chromosomes. *Evolution* 66, 3198–3208 http://dx.doi.org/10.1111/j.1558-5646.2012.01681.x
36 Úbeda, F. and Wilkins, J.F. (2011) The red queen theory of recombination hotspots. *J. Evol. Biol.* 24, 541–553
37 Segurel, L. *et al.* (2011) The case of the fickle fingers: how the *PRDM9* zinc finger protein specifies meiotic recombination hotspots in humans. *PLoS Biol.* 9, e1001211
38 Rebollo, R. *et al.* (2010) Jumping genes and epigenetics: towards new species. *Gene* 454, 1–7
39 Jurka, J. *et al.* (2011) Families of transposable elements, population structure and the origin of species. *Biol. Direct* 6, 44
40 Bohne, A. *et al.* (2008) Transposable elements as drivers of genomic and biological diversity in vertebrates. *Chromosome Res.* 16, 203–215
41 Zeh, D.W. *et al.* (2009) Transposable elements and an epigenetic basis for punctuated equilibria. *Bioessays* 31, 715–726
42 Brennecke, J. *et al.* (2008) An epigenetic role for maternally inherited piRNAs in transposon silencing. *Science* 322, 1387–1392
43 Khurana, J.S. *et al.* (2011) Adaptation to P element transposon invasion in *Drosophila melanogaster*. *Cell* 147, 1551–1563
44 Martienssen, R.A. (2010) Heterochromatin, small RNA and post-fertilization dysgenesis in allopolyploid and interploid hybrids of *Arabidopsis*. *New Phytol.* 186, 46–53
45 Erilova, A. *et al.* (2009) Imprinting of the Polycomb group gene MEDEA serves as a ploidy sensor in *Arabidopsis*. *PLoS Genet.* 5, e1000663
46 Ishikawa, R. and Kinoshita, T. (2009) Epigenetic programming: the challenge to species hybridization. *Mol. Plant* 2, 589–599
47 Kohler, C. and Kradolfer, D. (2011) Epigenetic mechanisms in the endosperm and their consequences for the evolution of flowering plants. *Biochim. Biophys. Acta* 1809, 438–443
48 Ishikawa, R. *et al.* (2011) Rice interspecies hybrids show precocious or delayed developmental transitions in the endosperm without change to the rate of syncytial nuclear division. *Plant J.* 65, 798–806
49 Lu, J. *et al.* (2012) Maternal siRNAs as regulators of parental genome imbalance and gene expression in endosperm of *Arabidopsis* seeds. *Proc. Natl. Acad. Sci. U.S.A.* 109, 5529–5534
50 Greiner, S. *et al.* (2011) The role of plastids in plant speciation. *Mol. Ecol.* 20, 671–691
51 Werren, J.H. (2011) Selfish genetic elements, genetic conflict, and evolutionary innovation. *Proc. Natl. Acad. Sci. U.S.A.* 108, 10863–10870
52 Fishman, L. and Willis, J.H. (2006) A cytonuclear incompatibility causes anther sterility in *Mimulus* hybrids. *Evolution* 60, 1372–1381
53 Frank, S.A. and Barr, C.M. (2003) Programmed cell death and hybrid incompatibility. *J. Hered.* 94, 181–183
54 Chou, J.Y. and Leu, J.Y. (2010) Speciation through cytonuclear incompatibility: insights from yeast and implications for higher eukaryotes. *Bioessays* 32, 401–411
55 Brucker, R.M. and Bordenstein, S.R. (2012) Speciation by symbiosis. *Trends Ecol. Evol.* 27, 443–451
56 Frank, S.A. and Crespi, B.J. (2011) Pathology from evolutionary conflict, with a theory of X chromosome versus autosome conflict over sexually antagonistic traits. *Proc. Natl. Acad. Sci. U.S.A.* 108, 10886–10893
57 Chase, K. *et al.* (2005) Interaction between the X chromosome and an autosome regulates size sexual dimorphism in Portuguese Water Dogs. *Genome Res.* 15, 1820–1824
58 Crespi, B.J. (2008) Turner syndrome and the evolution of human sexual dimorphsm. *Evol. Appl.* 1, 449–461
59 Good, J.M. *et al.* (2010) Widespread over-expression of the X chromosome in sterile F-1 hybrid mice. *PLoS Genet.* 6, e1001148
60 White, M.A. *et al.* (2011) Genetic dissection of a key reproductive barrier between nascent species of house mice. *Genetics* 189, 289–304
61 Mishra, P.K. and Singh, B.N. (2006) Genetic interactions underlying hybrid male sterility in the *Drosophila bipectinata* species complex. *Genes Genet. Syst.* 81, 193–200
62 Sackton, T.B. *et al.* (2011) Interspecific Y chromosome introgressions disrupt testis-specific gene expression and male reproductive phenotypes in *Drosophila*. *Proc. Natl. Acad. Sci. U.S.A.* 108, 17046–17051
63 Sweigart, A.L. (2010) The genetics of postmating, prezygotic reproductive isolation between *Drosophila virilis* and *D. americana*. *Genetics* 184, 401–410
64 Sweigart, A.L. (2010) Simple Y-autosomal incompatibilities cause hybrid male sterility in reciprocal crosses between *Drosophila virilis* and *D. americana*. *Genetics* 184, 779–787
65 Turelli, M. and Moyle, L.C. (2007) Asymmetric postmating isolation: Darwin's corollary to Haldane's rule. *Genetics* 176, 1059–1088
66 Meiklejohn, C.D. and Tao, Y. (2010) Genetic conflict and sex chromosome evolution. *Trends Ecol. Evol.* 25, 215–223
67 Hahn, M.W. *et al.* (2012) No evidence for biased co-transmission of speciation islands in *Anopheles gambiae*. *Philos. Trans. R. Soc. B: Biol. Sci.* 367, 374–384
68 Rieseberg, L.H. (2001) Chromosomal rearrangements and speciation. *Trends Ecol. Evol.* 16, 351–358
69 Noor, M.A.F. *et al.* (2001) Chromosomal inversions and the reproductive isolation of species. *Proc. Natl. Acad. Sci. U.S.A.* 98, 12084–12088
70 Gavrilets, S. (2004) *Fitness Landscapes and the Origin of Species*, Princeton University Press
71 Rundle, H.D. and Nosil, P. (2005) Ecological speciation. *Ecol. Lett.* 8, 336–352
72 Henikoff, S. *et al.* (2001) The centromere paradox: stable inheritance with rapidly evolving DNA. *Science* 293, 1098–1102
73 Brandvain, Y. and Haig, D. (2005) Divergent mating systems and parental conflict as a barrier to hybridization in flowering plants. *Am. Nat.* 166, 330–338
74 Leimu, R. and Fischer, M. (2008) A meta-analysis of local adaptation in plants. *PLoS ONE* 3, e4010

75 Hereford, J. (2009) A quantitative survey of local adaptation and fitness trade-offs. *Am. Nat.* 173, 579–588
76 Adams, C.S. (2005) Intraparental gamete competition provides a selective advantage for the development of hybrid sterility via meiotic drive. *Evolution* 59, 1229–1236
77 Telschow, A. *et al.* (2007) *Wolbachia*-induced unidirectional cytoplasmic incompatibility and speciation: mainland-island model. *PLoS ONE* 2, e701
78 Duesberg, P. *et al.* (2011) Is carcinogenesis a form of speciation? *Cell Cycle* 10, 2100–2114
79 Sanei, M. *et al.* (2011) Loss of centromeric histone H3 (CENH3) from centromeres precedes uniparental chromosome elimination in interspecific barley hybrids. *Proc. Natl. Acad. Sci. U.S.A.* 108, E498–E505
80 Matsubara, K. *et al.* (2011) Relationship between transmission ratio distortion and genetic divergence in intraspecific rice crosses. *Mol. Genet. Genomics* 286, 307–319
81 Jones, N. and Pasakinskiene, I. (2005) Genome conflict in the gramineae. *New Phytol.* 165, 391–409
82 Tao, Y. *et al.* (2007) A sex-ratio meiotic drive system in *Drosophila simulans*. II: An X-linked distorter. *PLoS Biol.* 5, 2576–2588
83 Phadnis, N. and Orr, H.A. (2009) A single gene causes both male sterility and segregation distortion in *Drosophila* hybrids. *Science* 323, 376–379
84 Ferree, P.M. and Barbash, D.A. (2009) Species-specific heterochromatin prevents mitotic chromosome segregation to cause hybrid lethality in *Drosophila*. *PLoS Biol.* 7, e1000234
85 Tang, S.W. and Presgraves, D.C. (2009) Evolution of the *Drosophila* nuclear pore complex results in multiple hybrid incompatibilities. *Science* 323, 779–782
86 Bayes, J.J. and Malik, H.S. (2009) Altered heterochromatin binding by a hybrid sterility protein in *Drosophila* sibling species. *Science* 326, 1538–1541
87 Brideau, N.J. *et al.* (2006) Two Dobzhansky-Muller genes interact to cause hybrid lethality in *Drosophila*. *Science* 314, 1292–1295
88 Hui, L. *et al.* (2006) The mouse t complex gene Tsga2, encoding polypeptides located in the sperm tail and anterior acrosome, maps to a locus associated with sperm motility and sperm-egg interaction abnormalities. *Biol. Reprod.* 74, 633–643
89 Dilkes, B.P. *et al.* (2008) The maternally expressed WRKY transcription factor TTG2 controls lethality in interploidy crosses of *Arabidopsis*. *PLoS Biol.* 6, 2707–2720
90 Walia, H. *et al.* (2009) Dosage-dependent deregulation of an AGAMOUS-LIKE gene cluster contributes to interspecific incompatibility. *Curr. Biol.* 19, 1128–1132
91 Shi, W. *et al.* (2005) Widespread disruption of genomic imprinting in adult interspecies mouse (*Mus*) hybrids. *Genesis* 43, 100–108
92 Vrana, P.B. (2007) Genomic imprinting as a mechanism of reproductive isolation in mammals. *J. Mammal.* 88, 5–23
93 Josefsson, C. *et al.* (2006) Parent-dependent loss of gene silencing during interspecies hybridization. *Curr. Biol.* 16, 1322–1328
94 Ungerer, M.C. *et al.* (2006) Genome expansion in three hybrid sunflower species is associated with retrotransposon proliferation. *Curr. Biol.* 16, R872–R873
95 Shan, X.H. *et al.* (2005) Mobilization of the active MITE transposons mPing and Pong in rice by introgression from wild rice (*Zizania latifolia* Griseb.). *Mol. Biol. Evol.* 22, 976–990
96 Metcalfe, C.J. *et al.* (2007) Genomic instability within centromeres of interspecific marsupial hybrids. *Genetics* 177, 2507–2517
97 Brown, J.D. *et al.* (2012) Retroelement demethylation associated with abnormal placentation in *Mus musculus* x *Mus caroli* hybrids. *Biol. Reprod.* 86, 88
98 Barr, C.M. and Fishman, L. (2011) Cytoplasmic male sterility in *Mimulus* hybrids has pleiotropic effects on corolla and pistil traits. *Heredity* 106, 886–893
99 Sambatti, J.B.M. *et al.* (2008) Ecological selection maintains cytonuclear incompatibilities in hybridizing sunflowers. *Ecol. Lett.* 11, 1082–1091
100 Ringo, J. *et al.* (2011) Bacteria-induced sexual isolation in *Drosophila*. *Fly* 5, 310–315