THE ROLE OF SELFISH GENETIC ELEMENTS IN EUKARYOTIC EVOLUTION

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'Selfish genetic elements', such as transposons, homing endonucleases, meiotic drive chromosomes and heritable microorganisms, are common features of eukaryotes. However, their importance in the evolution of eukaryotic genomes is still controversial. In this review, we discuss these diverse elements and their potential importance in the evolution of genetic systems, adaptation, and the extinction and birth of species.

FITNESS
A measure of the capacity to survive and reproduce.

SYMBIONT
An organism that lives in intimate contact (symbiosis) with another organism during most of its life.

SEGREGATION DISTORTION
Any distortion of meiosis or gametogenesis such that one of a pair of chromosomes in a heterozygote is recovered in greater than half of the progeny.

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The historical and still common view of the genome is that of a highly integrated and coordinated network that has evolved to produce a viable and reproductively successful organism. The reason for this apparent 'harmony' among genes is that most mutations that decrease the survival or reproduction of the organism are selectively eliminated, whereas those that increase the FITNESS of the organism become established in the genome. However, it is now recognized that a significant portion of the genome of any eukaryote is composed of 'selfish' or 'parasitic' genetic elements, which gain a transmission advantage relative to other components of an individual's genome, but are either neutral or detrimental to the organism's fitness[1,2].

In this review, we briefly outline the diverse types of selfish genetic element that have been identified and discuss the general 'rules' that govern their biology. We assess the extent to which they have gone beyond being philosophical curios — examples of how natural selection acts at the level of the gene — to being elements important for organismal design and evolution. In particular, we discuss their potential roles in host extinction, host speciation and the architecture of genetic systems. We discuss whether certain aspects of gene regulation have evolved as mechanisms to silence transposable elements. We then consider the extent to which transposable elements have been co-opted to adaptive host function and the extent to which cytoplasmic sex-ratio distorters have driven the evolution of sex-determination systems.

Diversity of selfish genetic elements

Selfish genetic elements represent a remarkably diverse group — some exist in multiple locations in the genome, others at unique sites, some are nuclear genes and others reside in organelle or SYMBIONT genomes. Transposable elements, for instance, use different 'strategies' to reproduce in the genome to increase their copy number. Conversely, SEGREGATION DISTORTERS are a class of genes that emerge from meiosis in more than one-half of the gametes produced by a heterozygote. Both of these strategies result in the spread of the element and both can damage the 'host'. Other potential examples of selfish or parasitic genetic elements include SUPERNUMERARY (B) CHROMOSOMES, heritable microorganisms and HOMING ENDONUCLEASES. Even mitochondrial and plastid organelles can evolve features that are detrimental to the organism but that enhance their own transmission. Selfish genetic elements have been categorized in many ways, but can be most usefully subdivided into four types (see below) according to the mechanism by which they spread.

Autonomous replicating elements. Mobile elements (FIG. 1) encode the ability to move to new positions in the genome and can therefore accumulate in genomes. They are widely accepted as being selfish genetic elements, as first proposed by Doolittle and Sapienza[3], and Orgel and Crick[4]. Previous studies had assumed that mobile DNA had some beneficial function for the organism. However, when Hickey[5]

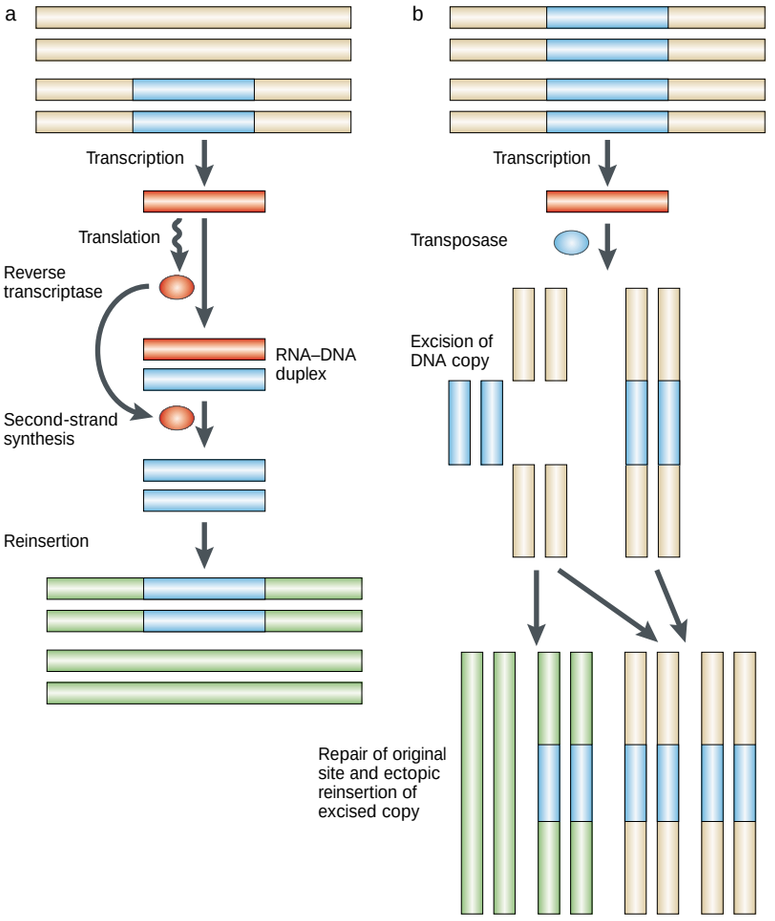


Figure 1 | **Types of transposable element. a** | Class I transposable elements transpose through an RNA intermediate. After the element is transcribed, the RNA copy is converted into DNA, frequently as a result of reverse transcriptase activity encoded in the element itself. This DNA copy now reinserts in the genome at an ectopic location. The figure shows long-terminal-repeat (LTR) retrotransposons (such as *copia* in *Drosophila* and *Ty1* in yeast) that have characteristic sequence motifs (LTRs) at either end. Non-LTR retrotransposons (such as mammalian LINES and SINES, the *Drosophila* I element), which do not have LTRs, transpose through a different mechanism. **b** | Transposition of class II elements involves DNA excision and homologous repair. Each class II element encodes a transposase, which excises the element from the chromosome. The point of excision is repaired using the sequence of homologue or sister chromatid as a template, which creates a duplicate of the transposable element. The excised copy is free to insert at an ectopic site within the genome. *P* and *hobo* in *Drosophila*, *Ac* in maize and *mariner* elements of many eukaryotes are class II transposable elements.

explored the population dynamics of transposons, he found that they can spread through outbred populations even if the excision and insertion events required for their transposition cause harmful mutations. Mobile elements can substantially contribute to the genome content. Transposable elements, for instance, comprise over 50% of the maize genome, 45% of the human genome and 15% of the *Drosophila Melanogaster* genome[3–5]. Although transposons might occasionally induce beneficial mutations, their spread is most parsimoniously explained by their ability to replicate in the genome as 'genomic parasites'[9]. Nevertheless, there is evidence that some transposons have been 'co-opted' by the genome for functional purposes (see REF. 10 and below).

Converting elements. GENE CONVERSION is a rare event and generally occurs in a minority of meioses[11]. However, there is a class of genes that encode the homing endonucleases, in which gene conversion occurs frequently and is heavily biased in one direction[12,13] (FIG. 2). Found in both organelle and nuclear genomes, these elements encode an endonuclease that introduces a double-stranded break at 15–20-bp recognition motifs. The break is not repaired by direct re-ligation, but by using the sequence that contains the homing endonuclease gene as a template. The end result is a conversion of the target sequence to one that contains the converting element. The repair also splits the recognition motif, thus preventing future self-cleavage. So, the homing endonuclease sequence is overrepresented among the gametes of heterozygous individuals and will increase in frequency, often to FIXATION.

Segregation distorters. Although meiosis is typically 'fair', in that each of the homologous sequences of a diploid have equal probability (50%) of ending up in functional gametes, some gene sequences are routinely overrepresented among the products of meiosis. This is referred to as MEIOTIC DRIVE or 'segregation distortion'[14]. Two well-studied examples are *Segregation distorter* (*Sd*), a gene found in an inversion on chromosome 2 of *Drosophila melanogaster* (FIG. 3) and the *t*-complex in mice[15].

Segregation distortion complexes are often found in inverted regions of chromosomes. This is probably because these systems frequently involve two loci — a driving locus and a sensitivity locus. Inversion protects against the decoupling of the drive and insensitivity alleles by recombination (which would lead to the production of self-destructive 'suicidal' chromosomes) and facilitates their initial spread. However, a consequence of their presence in inversions is that individuals that are homozygous for distorting genes can have reduced fitness. In the case of the *t*-complex in mice, for instance, certain *t*-alleles are homozygous lethal, and others are homozygous sterile owing to their coupling to deleterious recessive genes in the inverted complex. The presence of deleterious effects in the homozygous condition in part explains the persistent population polymorphism for *Sd* and *t* (REF. 15).

Segregation distorters occur in many species (for a review of meiotic drive, see REF. 14) and are likely to be very common[16], but they are difficult to observe unless detectable genetic markers are present and unless the driving element occurs polymorphically in a species. Segregation distorters are most easily detected when they occur on the sex chromosomes, because a sex-ratio bias is observed as a result of an excess of gametes with either the X chromosome (X drive against Y) or the Y chromosome (Y drive against X). Sex-chromosome drive has been observed in various organisms, including dipterans (flies), mammals and plants, and is likely to be widespread and common, although its incidence in non-model organisms is less well characterized[17].

SUPERNUMERARY (B) CHROMOSOME
A chromosome that is non-essential to organismal function and might be present in zero, one, two or more copies per individual.

HOMING ENDONUCLEASE
An enzyme that cuts DNA at a sequence motif and inserts a copy of its own gene into the cut site.

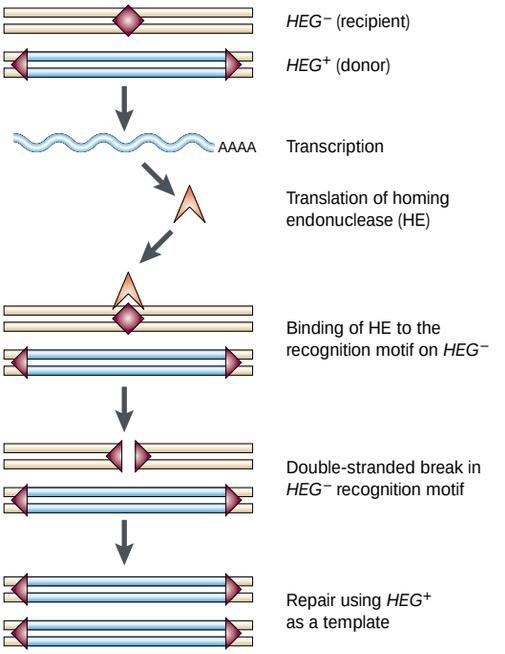


Figure 2 | **Homing endonucleases.** A donor allele, homing endonuclease gene (*HEG*)$^+$, encodes a homing endonuclease that introduces double-stranded breaks in 15–20-bp sequence motifs. The breaks are then repaired using the *HEG* donor sequence as a template, resulting in a gene conversion. The repair splits the recognition motif and therefore prevents future re-excision. The net result is the inheritance of the HEG in nearly all meiotic products.

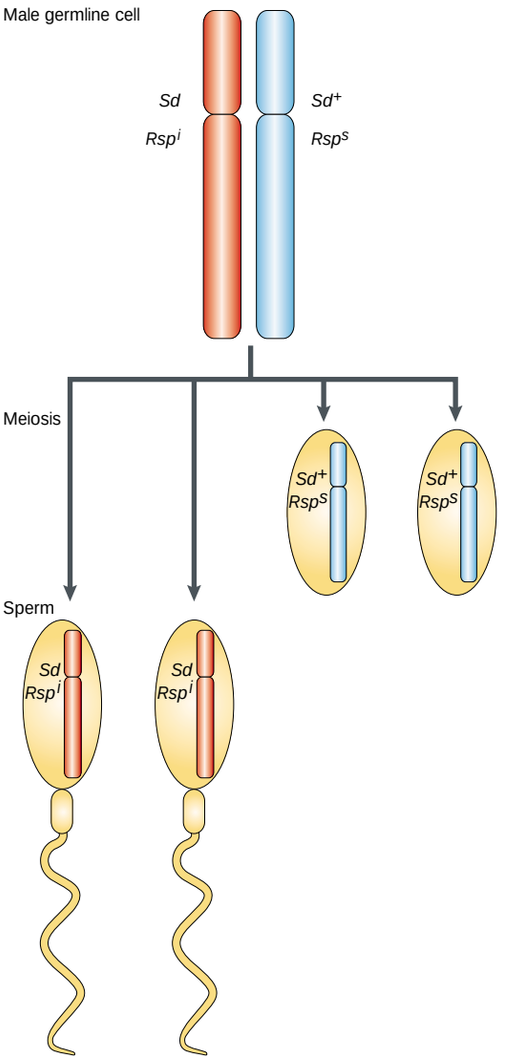


Figure 3 | **Model of *Segregation distorter* (*Sd*) action in *Drosophila melanogaster*.** In its simplest form, the system involves an interaction between two linked loci, *Sd* and *Rsp* (responder)[78–80]. The *Rsp* locus can harbour either the *Rsp*^{i} allele (insensitive to distortion by *Sd*) or the *Rsp*^{s} (sensitive to distortion by *Sd*). *Sd* produces a truncated version of the RanGAP nuclear transport protein, and its presence interferes with the normal processing of *Rsp*^{s}-bearing sperm, by mechanisms that are still unclear. *Sd* and *Rsp*^{i} are often found coupled together. If this is the case, and the homologous chromosome bears the sensitive allele *Rsp*^{s}, then sperm that bear *Rsp*^{s} degenerate and the chromosome that bears *Sd* and *Rsp*^{i} is inherited by up to 99% of all progeny. In the diagram, the male is heterozygous, bearing *Sd* with *Rsp*^{i} on one copy of chromosome 2, and *Rsp*^{s} and no copy of *Sd* (*Sd*$^+$) on the other. Four meiotic products are formed, but those that bear *Rsp*^{s} fail to mature. All functional sperm produced by the male bear both *Sd* and *Rsp*^{i}.

Supernumerary B chromosomes represent another class of segregation distorters. These chromosomes, which are widespread in eukaryotes, are not essential for organism function and can be present in one or more copies per individual. They spread through populations and persist by virtue of their capacity to be inherited by greater than 50% of progeny as a result of preferential segregation at meiosis, and through accumulation in mitotic events before gamete formation[18].

Post-segregation distorters. Some selfish elements reduce the frequency of non-carrier individuals after fertilization and the commencement of development. Several of these act by killing individuals that have not received the selfish element (TABLE 1) and are analogous to post-segregation-killing plasmids, such as pIK137 in *Escherichia coli* (REF. 19, but also see REF. 20 for an alternative view). The *Medea* locus (maternal-effect dominant embryonic arrest) in the flour beetle *Tribolium castaneum* involves a maternal effect allele that kills progeny that do not inherit the allele[21]. Although biochemical mechanisms are still unclear, they probably involve a modification of the egg (by protein or mRNA) that must be rescued by the presence of the *Medea* locus in the zygote. CYTOPLASMIC INCOMPATIBILITY, induced by the cytoplasmically inherited bacterium *Wolbachia* (which is widespread in insects, arachnids (spiders), crustaceans and nematodes), also involves a modification–rescue system[22,23]. However, in this case, uninfected zygotes are killed by a paternal effect from infected fathers, with a net increase in the frequency of infected individuals.

In some cases, these elements spread through PANMICTIC POPULATIONS, whereas others require structured populations or competition among siblings for resources (for example, *Medea*) for their spread.

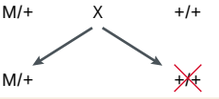
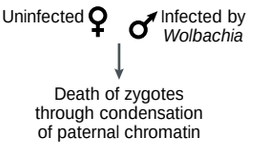
GENE CONVERSION
A non-reciprocal recombination process that results in an alteration of the sequence of a gene to that of its homologue during meiosis.

FIXATION
Increase in allele frequency to the point where all individuals in a population are homozygous.

MEIOTIC DRIVE
Distortion of meiosis such that one of a pair of chromosomes in a heterozygote is recovered in greater than half of the progeny. A subset of segregation distortion.

CYTOPLASMIC INCOMPATIBILITY
A sperm–egg incompatibility usually associated with *Wolbachia* infections. *Wolbachia* modify the host sperm in testes and the same strain of *Wolbachia* must be present in the egg to rescue this modification. Absence of rescue results in incompatibility and zygotic lethality.

Table 1 | Post-segregation distorters

Name	Gene location	Species affected	Consequences for the carrier	
Medea	Autosomal nuclear	*Tribolium castaneum* (beetle)[21]	Maternal effect, death of progeny from a heterozygous mother that do not inherit *Medea*.	
gp-9	Autosomal nuclear	*Solenopsis invicta* (fire ant)[81]	Individuals bearing *gp-9* will attack and kill individuals that do not carry it.	
Wolbachia (intracellular bacterium)	Cytoplasm	Many arthropods[24]	Cytoplasmic incompatibility. Paternal effect: death of zygotes formed after fusion of sperm from infected male with ova from uninfected female.	

Cytoplasmic incompatibility, for instance, involves the death of uninfected individuals, but this only indirectly increases the frequency of the agent that induces the incompatibility and there is no direct benefit. Population size and structure are important in determining the ease of invasion and increase of these elements[24].

Transmitting-sex enhancing elements. Nuclear genes are transmitted equally through male and female gametes, and selection in panmictic populations favours equality of allocation to sons and daughters. By contrast, cytoplasmic genes are often inherited uniparentally, most often through female gametes only. Selection on cytoplasmic genes favours the variants that increase allocation to the sex that can transmit them (females) over the sex that cannot (males)[25]. Many distortions of sex allocation are associated with genetic elements in the cytoplasm (TABLE 2); these include mitochondria that induce CYTOPLASMIC MALE STERILITY in plants, cytoplasmic microorganisms that feminize hosts, and PARTHENOGENESIS-inducing and male-killing microorganisms[26].

One interesting case of a nuclear element that promotes allocation to the sex that preferentially transmits it is the supernumerary *psr* (paternal sex ratio) chromosome of the PARASITOID wasp *Nasonia vitripennis*[27]. As in other HYMENOPTERA, males are haploid and females are diploid in this wasp species. Males with the *psr* chromosome produce functional sperm, but the paternal chromosomes (except *psr*) fail to condense properly in the first mitosis and are lost upon cell division. As a result, the fertilized (diploid) egg, which normally develops into a female, instead develops into a haploid male that also carries the *psr* chromosome. The genome of that male will also fail to be transmitted to his offspring when his sperm fertilize oocytes. Each generation, *psr* totally destroys the genome of its host, making it among the most extreme examples of selfish elements. Why is haploidization of fertilized eggs favoured? Unpaired supernumerary chromosomes typically have high transmission rates through haploid males (for example, near 100% in wasps) because male spermatogenesis in wasps is mitotic, but low transmission rates through females (for example, 10% in wasps) because the unpaired supernumerary chromosome segregates poorly in meiotic oogenesis. By converting females to males, *psr* ends up in the sex with higher supernumerary chromosome transmission rates.

Two 'rules' of selfish genetic elements

Although it is clear that selfish genetic elements are a very diverse group about which it is hard to generalize, there are two 'rules' that apply to many classes of element.

The first rule is that the diversity of selfish genetic elements in a species is correlated with the outbreeding rate of that species. Sexual reproduction enhances the spread of transposable elements and inbreeding decreases it[8,28]. When members of a population inbreed, heterozygosity decreases and opportunities for transmission between genomes also goes down. In inbred populations, selfish genetic elements are also more likely to be paired with their homologue, and therefore the frequency with which selfish behaviour is observed declines and the spread of the elements is impeded. For elements that increase in copy number in the genome, inbreeding increases the length of time for which deleterious effects associated with transposition are likely to be associated with the element, and this will again slow down or prevent their spread. It is therefore a general prediction that selfish genetic elements should be less common in inbreeding taxa.

This prediction is supported by empirical evidence. For example, the rate of spread of homing endonuclease genes in outbred populations of laboratory yeast is rapid, but does not occur in inbred strains (M. R. Goddard, D. Greig and A. Burt, unpublished data). Cross-species comparisons are also consistent with the theory. Bdelloid rotifers, an ancient asexual taxa, do not carry either LINE-like or GYPSY-like retrotransposons — elements that are present in all other animal taxa[29]. Furthermore, the incidence of supernumerary B chromosomes is greater in outbreeding than in inbreeding plants[30].

There are, of course, exceptions to this general principle. In the case of transposable elements, for instance, inbreeding in the laboratory is sometimes associated with increased transposition rate[31]. So, inbreeding associated with founder events might occasionally speed up

PANMICTIC POPULATION
A population in which the probability that any given male and female mate is equal for all individuals.

CYTOPLASMIC MALE STERILITY
Phenotype of male sterility in which the trait is carried on a cytoplasmically inherited gene. Occurs commonly in plants and is associated with mitochondrial mutations.

PARTHENOGENESIS
A form of reproduction in which eggs develop without being fertilized.

PARASITOID
An organism in which the adult is free living and lays eggs that hatch and develop in the body of another organism.

HYMENOPTERA
A large order of insects with four transparent wings that includes the bees, wasps, ants and sawflies.

Table 2 | Manipulations of host sex ratio by selfish elements

Selfish behaviour	Genetic element	Species affected	Description	References
Cytoplasmic male sterility	Mitochondria	Many angiosperms*	Death of anther (male) tissue in hermaphrodites	72
Parthenogenesis induction	*Wolbachia*	Range of Hymenoptera	Asexually produced haploid males have chromosome complement doubled, converting them to female development	82
Feminization	Microsporidia‡ *Wolbachia*	Amphipod§ and isopod‖ Crustacea; Lepidoptera¶	Individuals converted to female development, regardless of nuclear sex-determining factors	83
Male-killing	Range of bacteria Microsporidia	Many insects	Death of male embryos (in the case of bacteria) and male larvae (in the case of Microsporidia)	84

*Flowering seed plants. ‡Single-celled, protozoan life forms. §An order of mainly aquatic crustaceans with a laterally compressed body and many leg-like appendages. ‖An order of crustaceans that includes the woodlice and many aquatic forms. ¶An order of insects comprising the butterflies and moths.

the rate at which transposable elements accumulate in a lineage, rather than retard it. However, sexual reproduction (or infectious transmission) is necessary for the movement of transposons between lineages and therefore for their spread in a species.

A second rule of selfish genetic elements is that their phenotype is often shown in hybrids, but is not observed in within-population crosses. Discoveries of selfish genetic elements often follow from the emergence of a selfish phenotype either in a cross between members of closely related species, or in crosses involving individuals from different isolated populations within a species. Transposable elements[10,32] and meiotic drive[33] in flies, *Medea* in beetles[21], cytoplasmic male sterility in plants[34] and *Wolbachia*-induced cytoplasmic incompatibility in insects[35] have often been identified following the emergence of a new phenotype in hybrid inter-population or inter-species crosses.

There are two reasons why these phenotypes emerge in between-population crosses. First, selfish genetic elements sometimes spread to fixation in natural populations. If they are fixed and the homologue lost, then they cause no readily observable phenotype in the population, as the phenotype is directed only at non-carriers. However, crosses to naive populations (those that do not carry the given element) restore diversity and the phenotype of the selfish genetic element becomes evident once more. Second, selfish genetic elements might become repressed in populations. For transposable elements, this repression can be caused by the generation of non-autonomous elements, which can inhibit transposition of fully functional elements[36], or from nuclear repressors, such as the *flamenco* locus in *Drosophila*[37]. For other selfish genetic elements, suppression might also result from the spread of unlinked genes in the genome that inhibit the selfish phenotype. For the case of segregation distortion, unlinked mutations that prevent the action of the driving element will spread by natural selection, as these will increase the sperm number of the individual. If these are free of cost in the absence of the selfish phenotype, they might spread to fixation in the population, thereby preventing the action of the selfish genetic element. However, the driving phenotype will re-emerge in hybrid individuals who might lack repressor genes.

REPRODUCTIVE ISOLATION
The condition in which barriers prevent or strongly limit reproduction between populations. Reproductive isolation can occur in many ways, but always has the same effect: no or few genes are exchanged between populations.

HYBRID DYSGENESIS
Breakdown of organismal function after crosses involving individuals from different populations. An example is *P*-element-mediated dysgenesis, in which crosses between males from populations bearing *P* elements and females from populations in which they are absent is associated with gonadal dysfunction and elevated deleterious mutation rates.

Consequences for eukaryotic evolution

We now consider the evolutionary consequences of selfish genetic elements. Genomic parasites are a 'fact of life' for all eukaryotes. Their existence has been recognized for over 75 years. Evidence is now emerging that these parasitic genetic elements have had important roles in eukaryotic evolution. We mention some examples below, focusing on the potential role of selfish genetic elements in eukaryotic speciation, in extinction and in shaping the structure of genetic systems.

Host speciation. There is increasing interest in the possible role of selfish elements in REPRODUCTIVE ISOLATION and speciation in eukaryotes. For example, it has been speculated that HYBRID DYSGENESIS, induced by the transfer and release of transposable elements in hybrid crosses, could contribute to reproductive isolation[38]. One problem with this idea is that after crossing a species boundary, some transposons can quickly become established and regulated in the new host species, resulting in elimination of most hybrid dysgenic effects[10]. Frank[39], and Hurst and Pomiankowski[40], have proposed that the release of segregation distortion and/or cytoplasmic sex-ratio distortion in hybrids might contribute to hybrid sterility in a similar manner, although convincing empirical data do not yet support this model[41,42]. Transposable elements might also have a role in reproductive isolation by increasing the rate at which new chromosomal rearrangements (inversions and translocations) arise and by fixation in different populations of different chromosome rearrangements. Chromosome rearrangements after ectopic recombination are common in dysgenic crosses in the laboratory and there is evidence for their occurrence in wild populations. For example, there is an association between *P*-element insertion sites and inversion breakpoints in natural populations of *Drosophila willistoni*[43].

Box 1 | Transposable elements and gene-silencing mechanisms?

Various gene-silencing mechanisms observed in eukaryotes have been suggested to have evolved as mechanisms to reduce the activity of transposable elements. However, although these silencing mechanisms reduce transposable element activity, this does not mean that they evolved as a means to prevent transposable element activity. The genetic processes listed below might have other functions and the importance of transposable elements in their evolution thus remains contentious.

Repeat-induced point mutation (*RIP*) *in fungi*
In *Neurospora*, this involves the methylation and hypermutability of repeated gene sequences, causing the destruction of multicopy transposable elements. RIP is associated with C → T substitutions in repeated sequences after cytosine methylation. The methylation produces short-term transcriptional silencing and the subsequent mutation permanently disables transposition activity.

Methylation induced premeiotically (*MIP*) *in fungi*
In the fungus *Ascobolus immersus*, this involves the transcriptional silencing of multicopy DNA by methylation[58].

Repeat-induced gene silencing in flowering plants
Involves transcriptional silencing of multicopy DNA by methylation.

Methylation in vertebrates and plants
Methylation of cytosine residues might prevent transcription of transposable elements and evidence indicates that methylation is an adaptation to reduce the deleterious consequences of transposition. Conversely, the importance of methylation in the regulation of gene expression also makes this a viable hypothesis for the origin of methylation. Although the hypothesis that methylation evolved as a means of silencing transposable elements is both tenable and exciting, the primary force underlying the evolution of methylation remains unclear.

RNA interference
RNA interference (RNAi) leads to silencing of gene sequences by homologous RNA sequences, through a poorly understood mechanism that involves untranslated double-stranded RNA. Experimental evidence indicates that RNAi causes germline silencing of transposable elements in *Caenorhabditis elegans*.

Wolbachia are cytoplasmically inherited bacteria that are very widespread in insects (20–75% of species), arachnids, crustaceans and nematodes (for reviews see REFS 22,23). Recent data indicate that cytoplasmic incompatibility caused by *Wolbachia* could have a role in promoting reproductive isolation between closely related species, thus allowing divergence to continue and speciation to occur. Shoemaker *et al.*[44] have found that reproductive isolation between two mushroom-feeding species of *Drosophila* is enhanced by the presence of *Wolbachia* in one of the species. Generally, the unidirectional incompatibility that occurs when one species is infected is not sufficient to cause reproductive isolation between species, because GENE FLOW readily occurs in one direction and the bacteria are expected to move across the species boundary, infecting both species and eliminating cytoplasmic incompatibility between them. However, Shoemaker *et al.*[44] found that cytoplasmic incompatibility in one direction is coupled to other isolating mechanisms in the other (for example, mate discrimination), effectively eliminating gene flow between the species. Their study shows how *Wolbachia* can be a principal contributor to reproductive isolation in some systems. The second example involves bidirectional cytoplasmic incompatibility (bi-CI). Bi-CI occurs when two populations or species are infected with different *Wolbachia* strains that cause incompatibility in both directions. The parasitic insect genus *Nasonia* includes three closely related species, each infected with its own set of *Wolbachia* bacteria that cause bi-CI (REF. 45). The bi-CI has arisen early during speciation in this system, before the evolution of other common isolating mechanisms, such as HYBRID BREAKDOWN, hybrid inviability and hybrid sterility[46], indicating the potential of *Wolbachia* as an early speciation mechanism.

The idea that these inherited bacteria are an important isolating mechanism in nature is controversial. It is still unclear whether they provide sufficient isolation between incipient species to allow speciation and whether they are associated with speciation frequently enough to be important. Recent theoretical work indicates that even incomplete CI might be sufficient to maintain and permit genetic divergence between populations under biologically realistic conditions[47]. However, additional work is clearly needed to determine to what extent these bacteria have a role in arthropod (and nematode) speciation.

Host extinction. As early as 1967, Hamilton recognized that the fixation of sex chromosomes that cause meiotic drive could lead to host extinction. In principle, a population could become extinct through a shortage of males owing to a driving X chromosome spreading through the population, or from a lack of females after the spread of a driving Y chromosome[48]. Similar arguments apply to cases of mitochondria that cause cytoplasmic male sterility, and perhaps to sex-ratio-distorting inherited microorganisms that spread to extreme prevalence.

Extinction is not, however, a necessary outcome after invasion of a selfish sex-ratio distorter and might be avoided if the sex-ratio distortion is incomplete or if the element does not reach fixation in the population. Incomplete penetrance of distortion is most likely to allow population persistence, when the selfish genetic elements favour production of females, as a single male might maintain the fertility of several females simultaneously. Alternatively, frequency-dependent factors or autosomal resistance genes can maintain sex-ratio distorters at intermediate prevalence[49].

Although the causes of extinction represent a notoriously difficult subject of study, there is indirect evidence that sex-ratio-distorting strains can become fixed and therefore cause population extinction. There are three noteworthy studies that support this hypothesis. First, segregation-distorting sex chromosomes can spread to fixation and eliminate their hosts in laboratory populations. In an elegant experiment, Lyttle[50] created a new Y-drive system in *D. melanogaster*, using a translocation of *Sd* to the Y chromosome. When flies with this chromosome were placed into population cages, the driving Y chromosome increased to fixation in some populations, resulting in extinction owing to a lack of females. Second, male-killing *Wolbachia* in the butterfly species *Acraea encedon* and *Acraea encedana* can reach very high frequencies in natural populations,

GENE FLOW
Movement of genes from one population to another.

HYBRID BREAKDOWN
A post-zygotic isolating mechanism in which the first-generation hybrids are viable and fertile, but subsequent generations of hybrids are inviable or infertile.

Box 2 | Transposable elements and genome design

Transposable elements might have been important in genome design because of their ability to restructure chromosomes or because of their co-option into genetic processes.

Restructuring of chromosomes
Transposable elements might be important in inducing inversion and translocation of chromosomal segments in natural populations. These rearrangements are a result of ectopic recombination between homologous transposable element sequences scattered throughout the genome.

Construction of telomeres
Telomeres become shortened with every round of chromosome replication because DNA replication is inefficient at replicating chromosome ends. All organisms with linear chromosomes have mechanisms to extend telomeres and maintain their length. In *Drosophila*, telomere ends are constructed of *TART* and HetA class I transposable elements[73]. These are inserted after DNA replication to maintain telomere length. Phylogenetic analysis indicates a possibly more ancient link between telomeres and transposons. Telomerase, the enzyme that completes telomere extension in most eukaryotes, has a reverse transcriptase component that is structurally similar to the reverse transcriptase of non-LTR retrotransposons. It has been argued, therefore, that either retro-elements evolved from telomerase, or that telomerase evolved from retro-elements[74,75].

Somatic recombination mechanisms
The diversity of immunoglobulins in the vertebrate immune system represents an important aspect of the response to various antigens. Part of this diversity is generated somatically through *V(D)J* RECOMBINATION of vertebrates, which uses genetic shuffling to produce immunoglobulin variation. Two key genes involved in this process, *RAG1* and *RAG2*, show mechanistic similarities to the *mariner-TC1* superfamily of transposons and can affect transposition in a cell-free system[76,77]. These findings imply that a transposon insertion might have been co-opted (or domesticated) during the evolution of the vertebrate immune system, to provide a mechanism for creating high levels of variation in immunoglobulins.

INTRONS LATE MODEL
A model that proposes that introns evolved from transposon-like group II elements and that the spliceosome machinery evolved to mitigate their negative effects.

V(D)J RECOMBINATION
A specialized form of recombination that assembles the genes that encode lymphocyte antigen receptors from variable (*V*), diversity (*D*) and joining (*J*) gene segments.

resulting in females going unmated[51,52]. Finally, there are many observations of populations at fixation for *Wolbachia* strains that induce parthenogenesis[23]. If parasites that distort sexuality can spread to fixation, it is likely that those that feminize or kill male hosts might also do so. The only caveat here is that selection for resistance is stronger for a sex-ratio distorter than for a distorter of sexuality[53].

Although it is so far not possible to state that sex-ratio-distorting elements have caused population extinction, 30 years of research provide indirect support for Hamilton's idea that fixation of sex chromosomes can lead to host extinction. The rate at which invading elements drive their host to extinction is not known. The problem, of course, is that it is easier to study the systems in which selfish elements have not caused extinction than those in which they have.

Shaping the genetic architecture of eukaryotes. Selfish elements are ubiquitous in eukaryotic genomes and in many cases make up a large portion of the DNA in an organism. Selfish genetic elements have caught the attention of biologists seeking to explain principal changes in evolution, and aspects of genomic and developmental architecture. They have been proposed to be the force that underlies the initial evolution of sex, recombination, the uniparental inheritance of organelles, genome structure (for example, the INTRONS LATE MODEL), and many aspects of the design of organisms (for example, the diversification of sex-determination systems)[1,2,54–57]. In the following section, we discuss two areas in which selfish genetic elements have recently been proposed as an important evolutionary force: the role of transposable elements in the evolution of eukaryotic genomes and the role of sex-ratio distorters in the evolution of sex-determination systems.

Apart from their large sequence contribution to the genome, there are two interesting evolutionary 'responses' of genomes to the presence of transposons: evolution of mechanisms to suppress their transposition and the occasional co-opting of transposons for beneficial functions.

There is growing evidence that eukaryotes have evolved several mechanisms for suppressing transposons (and their viral cousins) in the genome (BOX 1). Examples include the repeat-induced point mutation (RIP) and methylation induced premeiotically (MIP) in fungi[58], as well as homology-dependent gene silencing[59], methylation suppression of transposon expression in various eukaryotes and possibly RNA interference (RNAi)[60]. RNAi is found in various organisms and involves the silencing of gene expression by homologous double-stranded RNA sequences[61]. RNAi is generally believed to have evolved as a defence against double-stranded RNA viruses; however, evidence from *Caenorhabditis elegans*[60] indicates that RNAi can cause germline silencing of transposons.

Widespread methylation of cytosine residues in the genome occurs in vertebrates and various plant species, and has been considered a pivotal event in the invertebrate–vertebrate transition, permitting gene silencing and therefore allowing expansion in gene number[62]. It has also been argued that the evolution of methylation was a result of selection to reduce the rate of transposable element activity and the incidence of their associated deleterious mutations[63,64]. There is evidence that retro-elements in humans are methylated more frequently than would be expected by chance[64] and that failure of methylation in wallaby hybrids is associated with widespread retro-element activation[65]. These observations are consistent with the hypothesis that methylation evolved as a means of repressing transposable elements, but do not rule out other hypotheses for the evolution of methylation.

Evidence is accumulating that occasionally genomes might 'co-opt' transposons for specific functions (see BOX 2 for examples and REF. 10). Examples include telomere maintenance and aspects of the vertebrate immune system. The scale of co-option of genes from transposable elements to genome function is unknown, but the initial analysis of the human genome sequence has indicated 47 potential cases of co-option[4]. These have largely derived from transposons with DNA-mediated mechanisms of transposition.

Transposons provide genetic material on which natural selection can act, and so it is not surprising that new beneficial functions for these sequences would evolve. This, however, should not be confused with the primary selective forces that resulted in their

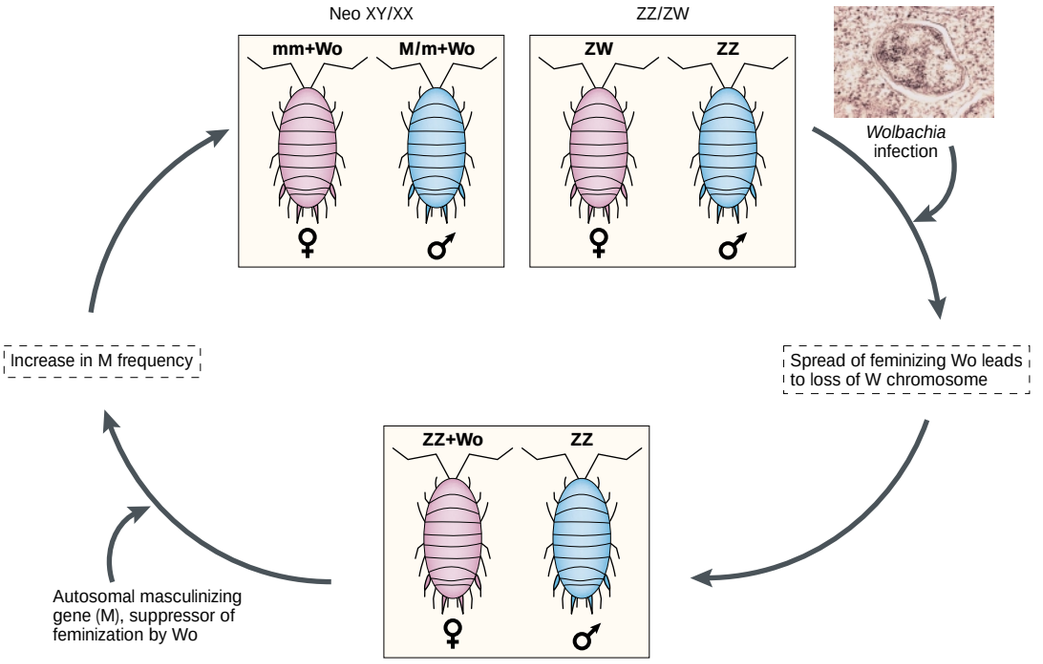


Figure 4 | **Model of the evolution of sex-determination system in *Armadillidium vulgare*.** Initially females are heterogametic (ZW) and there is no *Wolbachia* infection in the population. Invasion of maternally inherited feminizing *Wolbachia* (Wo) drives the Z chromosome to fixation, such that all individuals are ZZ, but individuals infected with *Wolbachia* develop as females and uninfected individuals as males. Subsequently, autosomal masculinizing genes (M) invade the population and prevent *Wolbachia*-mediated feminization. The initial female heterogametic system has now evolved into one in which sex is determined by a mixture of infection status with respect to feminizing *Wolbachia*, and nuclear autosomal genes, which repress feminization and act as new sex-determination loci. In this new system, it is the males that are heterogametic.

origin and best explain the maintenance of most transposons, and their ability to self-replicate despite their harmful effects on the host[5,6]. A still widely held opinion is that the 'function' of transposable elements is to produce variation for future evolution, that is, to promote 'evolvability'. At present, there are only a handful of examples of beneficial mutations caused by transposable elements, and to conclude that production of beneficial mutations is the 'function' of transposons confuses evolutionary cause and consequence[8,9]. Classical parasites (for example, viruses and bacteria) are believed to be important forces in the evolution of eukaryotes[66], but no one would propose that their function (that is, their reason for existence) is to cause eukaryotic evolution. Similarly, the self-replicating ability of genomic parasites (such as transposons) readily explains their maintenance in eukaryotes; we believe that the role of beneficial mutations in their maintenance is likely to be relatively unimportant.

Arguments have been made that the structure of eukaryotic genomes, including the abundance of transposons, repetitive DNA and introns, is designed for evolvablity. For this argument to be valid, a higher-level selective process (for example, selection at the level of species or taxon) is required. Variation in evolvability among ancestral taxa would have to have existed, with those taxa that show greater evolvability in turn having greater persistence and speciation rates. Such a hypothesis is plausible, but so far unsupported by evidence. Transposons and introns occur in nearly all higher eukaryotes, therefore it is not clear that their existence is due to selection for evolvability. Perhaps it can be argued that those taxa with a greater abundance of transposons or introns have greater evolvabilty. Such propositions could be testable by comparative methods. An alternative is that greater evolvability (if it exists) is merely an evolutionary consequence of these parasitic elements, not a selected feature. More precise formulations of evolvability hypotheses are needed for such ideas to be evaluated critically.

Evolution of sex-determination systems

Although it could be assumed that such a basic aspect of development as sex determination would be highly stable in evolution, the opposite is the case. Sex-determining mechanisms are incredibly diverse in plants and animals[67]. One possible explanation for this diversity is that sex determination is inherently unstable owing to conflicting selective pressures ('genetic conflict') between non-Mendelian sex-ratio distorters and Mendelian nuclear genes[23,68]. In many animals, cytoplasmically inherited microorganisms and mitochondria are uniparentally inherited through females and therefore are selected to bias sex ratio to that sex, whereas Mendelian nuclear genes are selected to produce a balanced sex ratio and therefore to suppress or counteract the action of

cytoplasmic elements. Segregation-distorting sex chromosomes that result in biased sex ratios can create strong selective pressures on Mendelian nuclear genes to counteract the distortion.

At present, two systems show how genetic conflict can shape sex-determining systems. The first is sex-determination-system evolution in the pillbug *Armadillidium vulgare* (FIG. 4). The 'normal' mode of sex determination in this species is female heterogamety (ZW females and ZZ males). However, many populations harbour a feminizing bacterium (*Wolbachia*) that converts genetic males into functional females[69]. The bacterial infection can achieve appreciable frequencies, often resulting in elimination of the W chromosome from the population. In some populations, a dominant masculinizing factor is present that overrides the action of the feminizing bacterium[70]. Theoretical studies indicate that the bias in population sex ratios caused by the feminizing bacterium selects for such masculinizing genes, and can effectively convert the population to male heterogamety (Mm males and mm females) from the previous female heterogametic form[71]. Nuclear resistance genes to transmission of the feminizing bacterium are also found in natural populations, and further show the selective conflicts between Mendelian nuclear genes and cytoplasmically inherited factors.

A second example is cytoplasmic male sterility (CMS). Many plants, including species of agronomic importance such as maize, have mitochondrial variants that prevent the formation of anthers or pollen. Because of their economic importance, the molecular mechanisms of several of these systems have been worked out and have been found to involve mutations or genetic rearrangements that create novel mitochondrial products that interfere with anther production[72]. A common feature is the presence of nuclear suppressors of CMS. As a result, a CMS phenotype depends on the relative frequencies of CMS haplotypes and nuclear suppressors of CMS. In some cases, the suppressors of CMS can become fixed in the species; the underlying genetic structure of sex determination is then a product of the conflict between cytoplasmic and nuclear genes.

The evidence is now overwhelming that 'genetic conflict' is an inherent feature of sex-determining systems. What is less clear is how often it has a role in the evolution of sex determination[68]. However, the two examples above do indicate how this might work.

Conclusions

Selfish genetic elements are common in eukaryotes. Transposons make up a large part of the genome of many eukaryotic species. Segregation-distorting chromosomes are widely distributed in eukaryotes, as are inherited microorganisms. Inherited organelles (mitochondria and chloroplasts), although clearly beneficial for the organism, can evolve phenotypes that are harmful to the organism but that enhance organelle transmission. In this review, we have discussed some of the evidence that indicates that selfish genetic elements have an important role in eukaryotic evolution. In some of these cases, the argument is reasonably compelling. In others, such as the hypothesis that methylation in mammals is an adaptation to prevent transposition, the explanation based on selfish genetic element repression is still one of several candidates, waiting to be evaluated. Growing evidence does indicate, however, that many interesting aspects of eukaryotic genomes, such as methylation and RNAi, could have evolved, or at least are at present maintained, as mechanisms to suppress multicopy selfish genetic elements. The potential role of genetic conflict between Mendelian nuclear genes and non-Mendelian sex distorters in sex-determination evolution is very real, although not yet fully evaluated. Beyond their importance in the design of genetic systems, selfish genetic elements are important at a higher level, as agents that might promote speciation or cause species extinction. We anticipate that research in the next decade will more clearly delineate the role of selfish genetic elements in eukaryotic genome evolution and in higher-order processes, such as speciation and extinction.

Links

DATABASE LINKS *Sd* | *t*-complex | *Medea* | *flamenco* | *RAG1* | *RAG2*

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Acknowledgements

J.H.W. thanks T. Eickbush for many interesting discussions on transposon evolution and S. Bordenstein for helpful discussions about heritable microbes and meiotic drive; G.D.D.H. thanks M. Goddard for discussions of homing endonuclease dynamics. We thank L. Sacchi, and C. Bandi for providing figures. G.D.D.H. is supported by a BBSRC David Phillips Fellowship. Research support for J.H.W. was provided by the US National Science Foundation.