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Editorial

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The evolutionary consequences of selfish genetic elements

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The traditional view of the genome was once that it is broadly cooperative, with all genes working together amicably to improve the success of the individual as a whole. Benefits to the individual, after all, benefit all the component genes, as fair Mendelian inheritance ensures that all the genes and alleles a parent carries are equally likely to be inherited by an offspring. However, more detailed studies of inheritance have shown that this rosy view of cooperation within the genome is untrue. Instead, many genes act selfishly, manipulating gametogenesis to bias transmission in their favor (Burt and Trivers 2006). This increases their representation in offspring at a cost to the fitness of the individual and the cooperative genes.

The existence of such selfish genetic elements has revolutionized our view of evolution, showing that cooperation between genetic elements to further the interests of the individual as a whole is not the only way forward (Werren 2011). Indeed, in this special column, Ågren (2016) reviews the history of how ideas about selfish genetic elements have interacted with broader evolutionary thought, particularly the contrast between the gene's eye view of evolution and ideas of multilevel selection.

Selfish genetic elements are expected to evolve whenever there is a conflict over transmission—where different genes are transmitted in different ways. For example, nuclear genes are typically inherited through all gametes, whereas genes in organelles are only inherited via eggs, not sperm or pollen, leading to conflicts between organelles and nuclear genes, such as selfish endosymbionts, pollen-killing chloroplasts, and mitonuclear conflict (Burt and Trivers 2006). There is enormous variety in the ways organisms arrange their genomes, package parts of these genomes into gametes, and mix gametes during sex. This diversity means there are likely to be large numbers of undiscovered selfish genes, acting in unexpected ways to manipulate gametogenesis and bias transmission in their favor.

Our understanding of selfish genetic elements and their influence on genome evolution is incomplete (Lindholm et al. 2016). Several outstanding questions are addressed in this special column: what is the prevalence of selfish genetic elements across organisms, what are their effects, how did they evolve, and how is conflict between the interests of selfish genetic elements and the rest of the genome resolved? Three very different systems are investigated: transposable elements in animals, a male meiotic driver in a mouse, and selfish mitochondria in a mussel.

One of the best known and widespread types of selfish genetic elements is transposable elements, genetic elements that insert themselves into other locations in the genome. Active and inactive transposable elements are present in nearly all genomes (Chénais et al. 2012), from archaea to humans. They are associated with costs to the host genome, including rearrangements, insertions and deletions across chromosomes, the disruption of genes and gene regulation, as well as an increase in genome size and associated transcription costs (Werren 2011). However, there are an increasing number of examples of evolutionary novelty associated with the insertion of transposable elements (e.g., Ding et al. 2016), adding to evidence that transposable elements can also benefit host genomes, at least under some circumstances (Chénais et al. 2012).

Luchetti and Mantovani (2016) investigate the conservation of features across distantly related taxa in one type of transposable element, SINEs (short interspersed nuclear elements). SINE structure includes the head and tail, which carry the key functional components that allow the SINE to jump to new locations, separated by a body domain in between. These SINE body domains are the focus of this study. The function of the body is unclear, but it does not seem to directly be involved in transposition. Despite this apparent lack of function, body domains can be extraordinarily highly conserved (called highly conserved domains, HCDs), with almost identical HCDs found in vertebrates and cephalopods, despite the enormous phylogenetic distance between these groups. With such similar HCDs found in such distantly related organisms, the theory that HCDs and SINEs are horizontally transmitted seemed quite well-supported (Werren 2011). In this study, the authors use data mining of published genomes to identify SINEs in a much broader range of taxa than previously achieved. Phylogenetic analysis of this larger dataset strongly contradicts the horizontal transmission theory. Instead, Luchetti and Mantovani (2016) suggest the current distribution of HCDs across the tree of life is mainly the result of vertical transmission—meaning that some HCDs have been conserved reliably in vastly different organisms, for 850 million years. This means that HCDs, despite being part of a selfish, manipulative and

damaging genetic element, and moreover being a part of that element that apparently has no function, have nevertheless persisted for as long as many of the fundamental genes that are vital to the biochemistry of most eukaryotic life.

The second paper explores resistance to the meiotic driving "*t* haplotype" chromosome found in mice (Silver 1985). The *t* haplotype does not follow the rule of random (Mendelian) inheritance of chromosomes. When heterozygous, it acts in developing sperm cells to harm the swimming ability of rival (non *t* haplotype carrying) sperm. It does so using a kind of poison—antidote system in which a "poison" affects all developing sperm, while only *t* haplotype sperm hold the "antidote" (Burt and Trivers 2006). The outcome in a mating cross is that nearly all of a female's eggs are fertilized by *t* haplotype sperm, instead of the usual 50% (Silver 1985; Lindholm et al. 2013). Such transmission distortion, called meiotic drive, is not limited to autosomes, as in this case, but can also affect sex chromosomes (Jaenike 2001). Sex chromosome drivers alter sex ratios of offspring, which bring into sharp relief the conflict between interests—the driver chromosome to increase transmission, and the carrier individual, to avoid fitness losses due to producing too many offspring of the most common sex. If the driver wins this conflict, this can potentially lead to the driver spreading to create a single-sex population (Price et al. 2010). In the mouse case, the *t* haplotype driver also has associated fitness costs: sons inheriting the *t* haplotype are very poor sperm competitors (Sutter and Lindholm 2015), and offspring homozygous for the *t* die prenatally (Silver 1985; Sutter and Lindholm 2015). Fitness loss caused by a driver will select for the evolution of driver suppressors—genes that prevent the driver manipulating reproduction, restoring transmission to close to Mendelian ratios (Burt and Trivers 2006). How suppression is achieved is often unclear. In some systems suppression can be biochemical, with suppressors rendering all sperm immune to the "poison" (Tao et al. 2007), but in many other systems there is no evidence this occurs (Burt and Trivers 2006). Sutter and Lindholm (2016) in this special column test whether suppression occurs behaviorally through mate choice against male carriers of the *t* haplotype. If females can avoid mating with males that carry the *t* haplotype, they protect their offspring from inheriting the *t*. Moreover, *t* mothers will reduce the risk that a *t* carrying male will father their offspring, causing embryo mortality.

However, how females might be able to discriminate between carriers and non-carriers is not obvious (Haig and Bergstrom 1995). A phenotypic signal closely associated with the driver is needed to identify it (Lande and Wilkinson 1999). In house mice, such a signal is potentially available in the form of unique major histocompatibility (MHC) alleles that are located within the *t* haplotype chromosome (Silver 1985; Lindholm et al. 2013). While MHC variants are important in resistance to disease (Unanue et al. 2016), they also influence body odor in mice (Yamazaki et al. 1990), thus *t*-linked MHC variants could provide an identity signal.

Sutter and Lindholm (2016) tested the preferences of female house mice in a serial mating context. Time to mating was compared between *t* carrier and non-carrier males, as females are expected to mate more rapidly with preferred than with non-preferred males. However, time to the start or completion of mating was not associated with the *t* carrier status of males or of females. These results accord with a previous experiment in which paternity results did not support a scenario of female mate choice against *t* carriers, using the same strain of mice (Manser et al. 2015). However, several studies by Lenington and colleagues did find evidence for female avoidance of *t* carrier males in choice tests (Lenington 1983; Coopersmith and Lenington 1992; Lenington and Coopersmith 1992). Why findings differ between these two research groups or *t* haplotype strains is still unclear, and highlights that much remains to be learned about meiotic drivers, even in the best known systems.

Interestingly, *t* carrier females in these mating trials were less likely to mate than non-carrier females. In a recent study of an X chromosome meiotic driver in *Drosophila subobscura*, Verspoor et al. (2016) found that carrier males were less likely to mate. These results are suggestive of widespread fitness effects on driver carriers that are still poorly understood.

The third paper by Milani et al. (2016) addresses selfish mitochondria. Mitochondria are also not transmitted in a Mendelian fashion, in most cases they are inherited from mother to offspring, with no transmission through the male. Thus, from the point of view of the mitochondrion, success in transmission to the next generation lies in optimizing female function (Hurst et al. 1996). This can explain why there are mtDNA variants that persist despite having harmful impacts on male aging, male success under sperm competition, and more broadly that create far more variation in male-biased gene expression than in female-biased gene expression (Innocenti et al. 2011; Camus et al. 2012; Yee et al. 2013). The evolution of male-specific mitochondria could be a way for males to dodge the fitness costs arising from female-biased selection. Male-specific mitochondria could specialize on improving male function, regardless of harm to females. However, having multiple mitochondrial types within an organism, competing over promotion of male versus female benefit and against each other, is predicted to be harmful (Hurst and Hamilton 1992). To protect against such harm, uniparental transmission of mitochondria is thought to have evolved. In mammals, for instance, this is achieved by specific machinery that break down paternal mtDNA (Luo et al. 2013; Sato and Sato 2013).

Maternal and paternal transmission of mitochondria has nonetheless evolved in some bivalve molluscs (Zouros 2013), called doubly uniparental inheritance. Males carry two types of mitochondria—a male (M) type localized in the testes but also present in male somatic tissues and a female type (F) that predominates in male somatic tissues, and is the only type found in females. Sperm carry the M type, eggs the F type. During zygote development, females lose the M type, while males become a mosaic, except in the gonads. Fascinatingly, M and F types show large divergence, with many predicted novel genes of unknown function, and the M type undergoing faster evolution (Zouros 2013).

How did doubly uniparental inheritance evolve, and why only in bivalve molluscs? Milani et al. (2016) tackled these questions by focusing on the genes *rphm21* from male mtDNA and *rphf22* from female mtDNA of the Manila clam *Ruditapes philippinarum*. Using the tools of *in situ* hybridization and immunohistochemistry, male-specific effects of *rphm21* are confirmed. Several lines of evidence indicate that *rphm21* and *rphf22* are more closely related to each other than to other M and F mtDNA novel genes. Thus, *rphm21* and *rphf22* have a recent common ancestor, and diverged when the mitochondrial genomes separated. What could have caused the differentiation? One clue comes from the observation that hermaphroditic bivalves do not have doubly uniparental inheritance (Breton et al. 2011), and Milani et al. (2014) suggest that *rphm21* plays a role in protecting M mitochondria from degradation. Another clue is evidence that *rphm21* is viral-derived (Milani et al. 2013a; Milani et al. 2014). Thus Milani et al. (2013b) proposed that endogenization of viral elements played a large role in the evolution of doubly uniparental inheritance, and that different viral elements

became independently incorporated into the mtDNA of different species. Here Milani et al. (2016) present a detailed model of how viral endogenization could have led to the evolution of the M and F mtDNA from a hermaphroditic ancestor.

Finally, Ågren (2016) reviews the interrelationships between the study of selfish genes, and the broader development of evolutionary theory. He argues that the gene's-eye view of selection, which revolutionized evolutionary biological thought in the 60s and 70s was vital for the widespread acceptance that some genes do not cooperate with the rest of the genome and instead act selfishly. He suggests that this perspective allowed the rapid development of selfish gene theory that occurred in that period. However, he points out that selfish genes have provided some of the best examples used to support one of the key rival perspectives on evolutionary biology, the idea of multilevel selection (Keller 1999). Selfish genes such as driving Y chromosomes provide clear examples of genetic elements that can spread through a population due to their selfish manipulation of gametogenesis, in which sperm carrying rival chromosomes are killed, but which may drastically reduce the fitness of the population as a whole (by reducing the number of females), potentially causing population extinction, or allowing rival species to outcompete it. Hence success at one level (gamete production) may be counteracted by failure at the population or species level (Burt and Trivers 2006). However, Ågren argues that both models have their values, and that a plurality of perspectives is vital, both for understanding evolution, but also for understanding selfish genes.

Selfish genes were first discovered almost a century ago. The appreciation by biologists that they are widespread and can have major impacts on evolution has been common for perhaps 50 years. Over the past 30 years, there has been a rapid expansion in the diversity of selfish genetic elements discovered since the onset of modern molecular biology (Werren et al. 1988; Burt and Trivers 2006; Werren 2011). Despite these decades of progress, our understanding of selfish genetic elements remains relatively poor. It is certain that vast numbers of undiscovered selfish elements exist, most functioning in species that have never been screened for such conflicts. Others may be inactive, representing historical conflicts, as seen in many of the transposable elements discussed by Luchetti and Mantovani (2016). Even systems that have been studied intensively for decades, such as the *t* haplotype in mice, continue to surprise us with novel discoveries, differences between strains, and controversies (Auclair et al. 2013; Sutter and Lindholm 2016).

One of the most rapidly advancing areas of research deals with the question of how genes of interest can be attached to selfish genetic elements with the aim of altering and/or controlling wild populations (Burt 2003; Esvelt et al. 2014; Gabrieli et al. 2014; Champer et al. 2016) and what the demographic and evolutionary consequences would be of the release of such gene drive systems (Backus and Gross, forthcoming; Bull 2015; Unckless et al. 2016). Knowledge from natural systems of selfish genetic elements has been key to many of these developments. However, studying selfish genetic elements is difficult. There is no easily detectable phenotype associated with a selfish element, so field studies are especially challenging (Lindholm et al. 2016). Detecting new selfish elements is hard, as it requires detailed knowledge of the element, or of inheritance through many families in a species. As a result, a relatively small number of key selfish elements are well studied. These include transposons and parasitic endosymbionts that are conserved and hence similar across species, and selfish elements that act in extremely well-studied organisms, such as the mice studied by Sutter and Lindholm (2016). But these are likely to be the tip of the iceberg. Theory suggests that where conflicts over transmission are possible, selfish genetic elements should evolve to take advantage of their cooperative peers, as seen in the biparental transmission of mitochondria seen by Milani et al. (2016). Fortunately, technological advances are making the large-scale genome sequencing of families, or of individuals and their gametes, easily affordable, and practical in relatively poorly studied groups. Once this becomes widespread, it is certain to reveal vastly more selfish elements, which will no doubt have new and fascinating methods of manipulating reproduction in their favor. Perhaps over the next 2 decades, this will give biologists a true understanding of just how much influence selfish genetic elements have had on the evolution of the organisms we see around us.

References

Ågren J, 2016. Selfish genetic elements and the gene's-eye view of evolution. *Curr Zool* **62**:659–666.

Auclair Y, König B, Lindholm A, 2013. A selfish genetic element influencing longevity correlates with reactive behavioural traits in female house mice *Mus domesticus*. *PLoS ONE* **8**: e67130.

Backus GA, Gross K. Forthcoming. Genetic engineering to eradicate invasive mice on islands: modeling the efficiency and ecological impacts. *Ecosphere*.

Breton S, Stewart D, Shepardson S, Trdan RJ, Bogan AE et al., 2011. Novel protein genes in Animal mtDNA: a new sex determination system in freshwater mussels (Bivalvia: Unionoida)? *Mol Biol Evol* **28**:1645–1659.

Bull JJ, 2015. Evolutionary decay and the prospects for long-term disease intervention using engineered insect vectors. *Evol Med Public Health* **2015**:152–166.

Burt A, 2003. Site-specific selfish genes as tools for the control and genetic engineering of natural populations. *Proc R Soc B* **270**:921–928.

Burt A, Trivers R, 2006. *Genes in Conflict: The Biology of Selfish Genetic Elements*. Cambridge (MA): Harvard University Press.

Camus MF, Clancy DJ, Dowling DK, 2012. Mitochondria, maternal inheritance, and male aging. *Curr Biol* **22**:1717–1721.

Champer J, Buchman A, Akbari OS, 2016. Cheating evolution: engineering gene drives to manipulate the fate of wild populations. *Nat Rev Genet* **17**:146–159.

Chénais B, Caruso A, Hiard S, Casse N, 2012. The impact of transposable elements on eukaryotic genomes: from genome size increase to genetic adaptation to stressful environments. *Gene* **509**:7–15.

Coopersmith C, Lenington S, 1992. Female preferences based on male quality in house mice: interaction between male dominance rank and *t*-complex genotype. *Ethology* **90**:1–16.

Ding Y, Berrocal A, Morita T, Longden KD, Stern DL, 2016. Natural courtship song variation caused by an intronic retroelement in an ion channel gene. *Nature* **536**:329–332.

Esvelt KM, Smidler AL, Catteruccia F, Church GM, 2014. Concerning RNA-guided gene drives for the alteration of wild populations. *eLife* **3**:e03401.

Gabrieli P, Smidler A, Catteruccia F, 2014. Engineering the control of mosquito-borne infectious diseases. *Genome Biol* **15**:535.

Haig D, Bergstrom CT, 1995. Multiple mating, sperm competition and meiotic drive. *J Evol Biol* **8**:265–282.

Hurst L, Atlan A, Bengtsson B, 1996. Genetic conflicts. *Q Rev Biol* **71**:317–364.

Hurst LD, Hamilton WD, 1992. Cytoplasmic fusion and the nature of sexes. *Proc R Soc B* **247**:189–194.

Innocenti P, Morrow EH, Dowling DK, 2011. Experimental evidence supports a sex-specific selective sieve in mitochondrial genome evolution. *Science* **332**:845–848.

Jaenike J, 2001. Sex chromosome meiotic drive. *Ann Rev Ecol & Syst* **32**:25–49.

Keller L, 1999. *Levels of Selection in Evolution*. Princeton (NJ): Princeton University Press.

Lande R, Wilkinson GS, 1999. Models of sex-ratio meiotic drive and sexual selection in stalk-eyed flies. *Genet Res* **74**:245–253.

Lenington S, 1983. Social preferences for partners carrying 'good genes' in wild house mice. *Anim Behav* **31**:325–333.

Lenington S, Coopersmith C, 1992. Genetic basis of mating preferences in wild house mice. *Am Zool* **32**:40–47.

Lindholm AK, Dyer KA, Firman RC, Fishman L, Forstmeier W et al., 2016. The ecology and evolutionary dynamics of meiotic drive. *Trends Ecol Evol* **31**:315–326.

Lindholm AK, Musolf K, Weidt A, König B, 2013. Mate choice for genetic compatibility in the house mouse. *Ecol Evol* **3**:1231–1247.

Luchetti A, Mantovani B, 2016. Rare horizontal transmission does not hide long-term inheritance of SINE highly conserved domains in the metazoan evolution. *Curr Zool* **62**:667–674.

Luo SM, Ge ZJ, Wang ZW, Jiang ZZ, Wang ZB et al., 2013. Unique insights into maternal mitochondrial inheritance in mice. *Proc Natl Acad Sci* **110**:13038–13043.

Manser A, König B, Lindholm AK, 2015. Female house mice avoid fertilization by *t* haplotype incompatible males in a mate choice experiment. *J Evol Biol* **28**:54–64.

Milani L, Ghiselli F, Guerra D, Breton S, Passamonti M, 2013a. A comparative analysis of mitochondrial ORFans: new clues on their origin and role in species with doubly uniparental inheritance of mitochondria. *Genome Biol Evol* **5**:1408–1434.

Milani L, Ghiselli F, Nuzhdin S, Passamonti M, 2013b. Nuclear genes with sex bias in *Ruditapes philippinarum* (Bivalvia, Veneridae): mitochondrial inheritance and sex determination in DUI species. *J Exp Zool* **320**:442–454.

Milani L, Ghiselli F, Maurizii MG, Nuzhdin SV, Passamonti M, 2014. Paternally transmitted mitochondria express a new gene of potential viral origin. *Genome Biol Evol* **6**:391–405.

Milani L, Ghiselli F, Passamonti M, 2016. Mitochondrial selfish elements and the evolution of biological novelties. *Curr Zool* **62**:687–697.

Price TA, Hurst GD, Wedell N, 2010. Polyandry prevents extinction. *Curr Biol* **20**:471–475.

Sato M, Sato K, 2013. Maternal inheritance of mitochondrial DNA by diverse mechanisms to eliminate paternal mitochondrial DNA. *BBA - Mol Cell Res* **1833**:1979–1984.

Silver L, 1985. Mouse *t* haplotypes. *Ann Rev Genet* **19**:179–208.

Sutter A, Lindholm AK, 2015. Detrimental effects of an autosomal selfish genetic element on sperm competitiveness in house mice. *Proc R Soc B* **282**:2015.0974. http://rspb.royalsocietypublishing.org/content/282/1811/20150974.

Sutter A, Lindholm AK, 2016. No evidence for female discrimination against male house mice carrying a selfish genetic element. *Curr Zool* **62**:675–685.

Tao Y, Masly J, Araripe L, Ke Y, Hartl D, 2007. A *sex-ratio* meiotic drive system in *Drosophila simulans*. I. An autosomal suppressor. *PLoS Biol* **5**:2560–2575.

Unanue E, Turk V, Neefjes J, 2016. Variations in MHC Class II antigen processing and presentation in health and disease. *Ann Rev Immunol* **34**:265–297.

Unckless RL, Clark AG, Messer PW, 2016. Evolution of resistance against CRISPR/Cas9 gene drive. *bioRxiv*. doi:http://dx.doi.org/10.1101/058438.

Verspoor R, Hurst GDD, Price TAR, 2016. The ability to gain matings, not sperm competition, reduces the success of males carrying a selfish genetic element in a fly. *Anim Behav* **115**:207–215.

Werren JH, 2011. Selfish genetic elements, genetic conflict, and evolutionary innovation. *Proc Natl Acad Sci* **108**:10863–10870.

Werren JH, Nur U, Wu C-I, 1988. Selfish genetic elements. *Trends Ecol Evol* **3**:297–302.

Yamazaki K, Beauchamp G, Bard J, Boyse E, 1990. Single MHC gene mutations alter urine odour constitution in mice. In: MacDonald D, Müller-Schwarze D, Natynczuk S, editors. *Chemical Signals in Vertebrates*. Oxford: Oxford University Press, 255–259.

Yee WKW, Sutton KL, Dowling DK, 2013. *In vivo* male fertility is affected by naturally occurring mitochondrial haplotypes. *Curr Biol* **23**:R55–R56.

Zouros E, 2013. Biparental inheritance through uniparental transmission: the doubly uniparental inheritance (DUI) of Mitochondrial DNA. *Evol Biol* **40**:1–31.