Nothing in Genetics Makes Sense Except in Light of Genomic Conflict

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Abstract

Examples of genomic conflict were apparent soon after the inception of the field of modern genetics. Despite these early discoveries, the relevance of genomic conflict to the core principles of genetics has been largely unappreciated. In this synthetic review I will describe why knowledge of the logic and diverse forms of genomic conflict is essential to understanding all subfields of genetics. Because there are so many ways in which some parts of all prokaryotic and eukaryotic genomes can evolve to gain a reproductive advantage at the expense of other parts, the prevalence of genomic conflict is universal, and it influences all aspects of genetic form and function.

INTRODUCTION

When Morgan, Sturtevant, Muller, and Bridges launched in 1915 the modern era of genetics by publishing their seminal book, *The Mechanism of Mendelian Heredity*, the genome of eukaryotes was envisioned to be a hereditary "blueprint" consisting of indivisible genes linearly arranged on chromosomes and containing only the information needed to transform a fertilized egg into a functional adult. As advances in mapping and sequencing technology allowed the "black box" of the genome to be illuminated, its structure was found to be far from this concise blueprint-like expectation. Like the "indivisible" atoms studied by physicists, genes were found to be composed of subunits (exons) that were separated by intervening sequences (introns; Gilbert 1978). Far from being stably arranged side-by-side along the length of chromosomes, genes were observed to sometimes "jump" to new locations (McClintock 1950) and to be embedded in a genetic graveyard consisting of the carcasses of decaying transposable elements (TEs) that sometimes far outnumber the genes coding for an organism's anatomical/physiological phenotype (reviewed by Aziz et al. 2010). In addition, genomes were found to be populated with a wide diversity of active parasitic TEs that contributed importantly to the mutation process, reproductive incompatibilities, and ectopic recombination leading to aneuploid gametes (reviewed by Lynch 2007). In some special cases, however, TEs were found to have become "domesticated," contributing to novel adaptations like telomere replication and new patterns of gene expression (reviewed by Bourque 2009). Many genes were also found to be silent or active depending on their parent of origin (Haig 1993), and some genes "cheated" by violating Mendel's laws of segregation, causing them to be overrepresented among the pool of functional gametes (Sandler & Novitski 1957). Alleles of some genes were even found that killed sibling embryos if they did not carry those same alleles (reviewed by Burt & Trivers 2006). All of these surprising attributes of the genome's architecture (and many others not described in this brief overview) were a consequence of past and present reproductive conflicts between different parts of the genome.

Although discovered early on in the study of genetics, throughout most of its history the concept of genomic conflict has been relegated to the role of an odd curiosity (like a two-headed snake in an old-time carnival "freak show") with little fundamental significance to the core principles of the field. More recently, genomic conflict has emerged as an important contributor to fundamental processes like mutation, gene expression and replication, genomic architecture, adaptation, and speciation, as well as to applied areas like mammalian cloning and vector control (reviewed by Werren 2011).

An implicit assumption of the founders of evolutionary genetics during the modern synthesis was that genes evolve adaptively in response to (*a*) the external physical and biotic environment and (*b*) the internal networks of integrated cellular, physiological, and anatomical structures needed to make a functional organism (Huxley 1942). Missing from this list is adaptation in response to selfish genomic elements that reproduce at the expense of the fitness of the organism as a whole or of other genomic regions within the genome.

In this review I will extrapolate from the theme of a classic paper written by Theodosius Dobzhansky (1973), "Nothing in Biology Makes Sense Except in Light of Evolution." The parallel statement—substituting genetics for biology and genomic conflict for evolution—is the theme of this review. The idea that genomic conflict has contributed to many genetic features is not new, so this synthetic review builds on previous reviews, especially those of Hurst & Werren (2001), Arnqvist & Rowe (2005), Burt & Trivers (2006), and Werren (2011).

In what follows, I propose that the importance of genomic conflict has been grossly unappreciated in the field of genetics and that modern texts of genetics are missing a crucial chapter on genomic conflict that should be placed at the very beginning of every text. Without first introducing

students to the logic and prevalence of genomic conflict, virtually nothing in the remainder of the genetics text will truly make sense. By "make sense" I mean an understanding of both the proximate "how" a genetic phenomenon operates today and also the ultimate "why" it evolved its extant properties. To this end, in the following sections I use the major chapter headings of a typical modern eukaryotic genetics text to organize this review, thus documenting the fundamental importance of genomic conflict in essentially all subdisciplines of the field. Although space constraints preclude making the same arguments for a prokaryotic genetics or evolution text, the same logic applies. As a preamble, I first make clear what is meant by the term genomic conflict.

WHAT IS GENOMIC CONFLICT?

Genomic conflict occurs when one part of the genome gains a reproductive advantage at the expense of one or more other parts, excluding the intrinsic advantage/expense duality that must occur when one allele is favored over another by simple individual-level selection (selection$_{SIL}$) or the equivalent duality when there is mutualistic coevolution among interacting loci, as described below. I use the term selection$_{SIL}$ to mean selection that increases the fitness of the organism as a whole, and in both sexes when they are present. Genomic parts can be (*a*) different genetic elements within a single individual (e.g., mitochondrial and nuclear genes), (*b*) different genes in separate individuals of the same species (e.g., functionally paired genes that contribute to alternative outcomes of an interaction trait—like the decision to mate), or (*c*) the same genomic region in males and females when there is opposing selection between the sexes.

Consider two different parts of the genome that we arbitrarily call A and B. As an initial benchmark, suppose that there is no genomic conflict between A and B; e.g., A codes for a hormone and B its receptor. If a new mutation at A ($A \rightarrow A'$) was favored by selection$_{SIL}$ and its accumulation led to the recruitment of a new mutation at B ($B \rightarrow B'$, whose gene product better bound the A'-coded hormone), then although A' gained a reproductive advantage at the expense of A and B, no genomic conflict occurred—only canonical individual-level selection occurred at each interacting locus leading to their mutualistic coevolution.

To illustrate genomic conflict, first suppose that A and B are located in different functional parts of the genome of the same individual. For example, suppose that A_{Mit} is a mitochondrial gene and B_{Nuc} is a nuclear gene. In most species, A_{Mit} would be propagated over multiple generations exclusively through the matriline because mitochondria are transmitted via eggs to both sons and daughters, but mitochondria do not further reproduce through sperm once in males. By contrast B_{Nuc} is propagated through both the matriline via eggs and the patriline via sperm. Counterintuitively, a mutation in A_{Mit} that was lethal to males but not harmful to females would have a selective advantage when brothers and sisters compete for shared limiting resources; e.g., such a mutation might retain its normal mitochondrial function but, through pleiotropy, disrupt the male-limited dosage compensation pathway of *Drosophila*. The mutation would be favored by selection, despite its lethality in males, because it would benefit the sisters that propagate it by reducing competition with the nonpropagating brothers that it kills. Such a mitochondrial mutation can have a net harmful effect on the organism as a whole, and hence B_{Nuc}. To see why, we need to do some simple bookkeeping. Suppose that lack of competition from brothers increased the fitness of sisters by 50%. From the perspective of a mother carrying the mutation A_{Mit}, her nuclear genes (including B_{Nuc}) gain fitness through her daughters' elevated fitness (50% more fit) but lose fitness through her dead sons (100% less fit). The net fitness effect is negative ($0.5 \times 0.5 - 0.5 \times 1.0 = -0.25$). In this case the mutation would cause intraindividual genomic conflict because it increases the fitness of one part of a mother's genome (A_{Mit}) while decreasing the fitness of B_{Nuc} and all other nuclear genes, except those on a nonrecombining W sex chromosome

in ZZ/ZW species. The same logic would apply to a similar mutation in a vertically transmitted cytoplasmic endosymbiont (e.g., *Wolbachia*) that is propagated only through the matriline.

Next, suppose that *A* and *B* are two alleles at a single locus. If *A* increases because (*a*) it was favored by selection$_{SIL}$, (*b*) the forward mutation rate producing it was faster than the back-mutation rate destroying it, (*c*) immigration brought in the allele faster than emigration removed it, or (*d*) chance fluctuations boosted its frequency (genetic drift), then no genomic conflict is occurring; this constitutes only classical evolutionary change. But if, for example, *A* increases by causing *B* to be shunted into a polar body during female meiosis and itself into the functional ovum more than 50% of the time (i.e., by meiotic drive), then this phenotype represents intraindividual genomic conflict. Here *A* gains a transmission advantage not because it increases the fitness of the organism as a whole, but because it selfishly harms allele *B* by increasing *B*'s probability of segregating to a dead-end polar body, i.e., by effectively "cheating" on Mendel's law of random segregation. Comparable examples of this sort of genomic conflict include alleles that kill noncarrier sperm (segregation distorters), siblings (zygotic drivers), genomic haplotypes (paternal genome loss), or cell lineages (reviewed by Burt & Trivers 2006).

Finally, suppose that A_{TE} is a TE and B_{Nuc} is a nuclear gene. Active TEs transpose to new genomic positions in addition to persisting at their original location; i.e., on average, they reproduce faster than the rest of the genome across a generation. This reproductive advantage reduces the fitness of the rest of the genome and leads to intraindividual genomic conflict when (*a*) transposed copies disrupt the function of one or more genes at or near the insertion site and/or (*b*) too many copies of TEs reduce the efficacy of replication, thereby lowering fitness of the organism as a whole. Other selfish elements that cause intraindividual genomic conflict by reproducing at the expense of the organism as a whole include homing endonucleases, which are TE-like sequences that insert copies of themselves into only highly specific DNA sequences and thereby cause insertional inactivation, and supernumerary B chromosomes, which are dispensable chromosomes that increase their copy number across generations and—when abundant or present in an odd copy number—reduce growth rate and/or fecundity (reviewed by Burt & Trivers 2006).

Intralocus sexual conflict is the second major category of genomic conflict. In this case, *A* and *B* are alleles at a locus that influence the same phenotypic character in both sexes, but the optimal allele differs between the sexes. One allele, say *A*♂, produces a phenotype closer to the male optimum and the other allele (*B*♀) closer to the female optimum. For example, consider a bird in which only females raise the young. Suppose that the optimal coloration for females (coded by *B*♀) is a drab green that helps to conceal mothers while incubating their brood, whereas the optimal coloration for males (coded by *A*♂) is a brighter hue that increases their attractiveness during courtship. As a consequence of such sex-specific selection, the optimal allele differs between the sexes and adaptation by one sex (i.e., increased frequency of the allele that produces a phenotype closer to that sex's optimum) is at the expense of the adaptation of the other sex. The allele that "wins" in intralocus genomic conflict, and increases to fixation, is usually the one with the larger selection advantage, causing a maladaptive phenotype to develop in the sex favoring the "losing" allele (Rice 1984). Alternatively, both alleles may sometimes persist as a balanced polymorphism, in which case both sexes are harmed because some individuals of each sex sometimes express the allele that is suboptimal for it. Intralocus sexual conflict can be resolved in several ways, including the evolution of (*a*) sex-specific gene splicing, (*b*) different expression profiles for the same gene in males and females, and/or (*c*) gene duplication followed by sex-limited gene expression at the duplicated loci (Stewart et al. 2010).

Interindividual genomic conflict occurs when two nonallelic parts of the genome (usually nuclear genes) mediate interactions between individuals and coevolve in an antagonistic manner that is conceptually similar to that between enemies, such as host and pathogen. This type of genomic

conflict can occur between members of the same sex (in the context of contests, like fighting and bluffing during disputes over resources; Rice & Holland 1997), but the most widespread form occurs between the sexes in the context of mating (Parker 1979), in which case it is called interlocus sexual conflict. The foundation for the conflict is an interaction trait; i.e., the trait is influenced by both a male and a female, usually in the context of a dyad, such as the decisions of whether or not to mate and how many offspring to produce (and how much to invest) in a brood after mating. When the optimum for the interaction trait differs between the sexes, males are expected to evolve to move the trait toward their optimal value, and conversely, females toward their optimum.

For example, suppose that mutations at one locus (A_{sem}) influence the interaction trait by coding for a seminal fluid protein that enters the female's blood stream and acts as a pheromone that boosts her fecundity rate, moving it toward the male's optimum (higher rate) but away from the female's optimum (lower rate). Further suppose that mutations at another locus in females (B_{recept}) influence the interaction trait by coding for changes to the pheromone's receptor that reduce its sensitivity and thereby cause it to resist up-regulation of fecundity rate by the male's pheromone. The seminal fluid protein sex peptide and its receptor in *Drosophila* species have the requisite interacting features for such interlocus sexual conflict (Wigby & Chapman 2005, Wolfner 2009). Adaptation at the A_{sem} locus would select for counteradaptation at the B_{recept} locus, so the A_{sem} and B_{recept} loci would be expected to antagonistically coevolve in a manner analogous to that between virulence genes in pathogens and resistance genes in hosts. Empirical studies indicate that males and females have different optima for many interaction traits associated with mating and reproduction (reviewed by Arnqvist & Rowe 2005); hence, there is a broad scope for interlocus sexual conflict.

A MARCH THROUGH THE CHAPTERS OF A EUKARYOTIC GENETICS TEXT

To develop the logic of the following sections, consider the way in which the basic organization of the cell and its replication is commonly introduced. Within one of the early chapters in most genetics textbooks is a schematic description of the two major genetic compartments of the cell (nucleus and cytoplasm) and how the hereditary material within them (chromosomes and mitochondrial/chloroplast genomes) is distributed to daughter cells during meiosis. Here it is pointed out in a matter-of-fact way that autosomal genes are distributed to both the matriline and patriline; the Y (W) sex chromosome is restricted to the patriline (matriline); and the mitochondrial/chloroplast genome, and the genomes of any cytoplasmic endosymbionts, are restricted to the matriline. These asymmetries in transmission are generally described as a simple consequence of the mechanics by which the cellular components are distributed to gametes during meiosis and gametogenesis, with no special significance or consequences other than the direction of flow of genes and alleles through pedigrees. Yet as I review more fully in later sections, these fundamental asymmetries have widespread and important genetic consequences, leading to mitochondria that commonly kill developing pollen in hundreds of species of plants, endosymbionts that kill nonpropagating descendants in thousands of insect species, and sex chromosomes that kill each other in species as diverse as flies and mammals. The fact that genomic compartments are transmitted differently across generations guarantees that different parts of the eukaryotic genomes will interact more like enemies at war than like finely coordinated gears in a well-engineered watch.

Space constraints do not permit me to elaborate on all the ways that genomic conflict influences different aspects of genetics in each of the following sections. Instead I provide one or a few examples to illustrate the importance of genomic conflict in all of the major subdisciplines of genetics.

Mendelian Inheritance

Mendel's "laws" of inheritance are used in essentially all introductory textbooks of genetics as a foundation on which to build the historical and conceptual framework of the field. The first law is that the two genetic elements (now known to be alleles of a gene) that influence a trait in a diploid individual are transmitted symmetrically during reproduction, such that each is transmitted to half of the gametes, and hence to half the offspring (with the exception of random deviations due to sampling error). The mechanism responsible for this law was later shown to be the symmetry of the cellular mechanisms by which chromosomes are randomly assembled on the metaphase plate and then distributed to daughter cells (gametes) during the process of meiosis.

Most students find this mechanical explanation to be highly instructive and compelling because it provides a simple and intuitively pleasing explanation for Mendel's first law. Clearly the cellular mechanics of meiosis are the predominant feature underlying Mendel's first law. But is this explanation, presented as the sole determinant of allelic segregation to gametes, too naive, and therefore misleading, for even an introductory student? Does it set the stage for thinking about genetics in the wrong way? If it is possible for an allele (or a neighboring linked gene) to have characteristics that cause it to be transmitted to >50% of offspring, then such an allele would have a reproductive advantage and accumulate, causing Mendel's first law to be violated.

We now know that there are many ways that alleles have in fact evolved to break Mendel's first law, including biased gene conversion, meiotic drive, segregation distortion, germ line stem cell drive, and zygotic drive (reviewed by Burt & Trivers 2006). These features, though little appreciated as important and widespread genetic phenomena until long after Morgan and colleagues' pivotal book, are not so rare as to be insignificant. For example, in humans, transmission distortion at 7 different genes containing microsatellites has been reported (Dean et al. 2006). Recent evidence indicates that there are at least three different segregation distorters on the X chromosome alone of *Drosophila simulans* (which, unlike *Drosophila melanogaster*, has the close relatives needed to uncover extant but currently suppressed segregation distorters) and possibly another distorter on the Y (Dermitzakis et al. 2000, Montchamp-Moreau & Cazemajor 2002, Tao et al. 2007, Meiklejohn & Tao 2010). In maize, every one of the chromosomes carries 1–4 recombination knobs capable of causing meiotic drive (Buckler et al. 1999) and there is widespread evidence that centromeres across a wide range of taxa rapidly evolve to gain a transmission advantage during meiosis in females (Malik & Henikoff 2009). Zygotic drivers have been uncovered in mice, beetles, and flies, and biased gene conversion is common in all species that have been screened (reviewed by Burt & Trivers 2006). Although most genes probably cannot code for phenotypes leading to strong transmission distortion, their linkage to other genes that can code for this phenotype (centromeres, meiotic drivers, segregation distorters, or zygotic drivers) will lead to biased Mendelian segregation over large portions of the genome.

What is intriguing is that Mendel's first law usually does hold (at least to a close approximation) despite the ability of genes to evolve to break the law in so many different ways. Genetics and evolution are intrinsically linked because it is evolution that built the form and function of genetics (Dobzhansky 1973). Genomic conflict is an integral part of meiosis and Mendel's laws because meiosis evolved not just to distribute genes to gametes (and offspring) but also to stop genomic conflict from disrupting this critical step in the reproductive process.

Dominance and Epistasis

Because diploid organisms have two alleles per locus and more than one locus can influence the same trait, the way in which alleles at the same and different loci interact to produce a phenotype is

a fundamental concept in genetics. In their simplest forms, dominant versus recessive alleles, these interactions can be understood based on simple chemical principles, like enzyme kinetics, without reference to genomic conflict. However, many common, but more complex, genetic interactions are intrinsically associated with genomic conflict.

For example, at some genes one allele is always silent and the other is expressed, but with no relationship to dominance because the silencing of an allele depends not on its DNA sequence but on its parent of origin, i.e., imprinted genes. There is now compelling evidence that imprinting influences the level of nutrient transfer between mother and offspring and that it has evolved in response to genetic conflict between male and female parents: Paternal imprints increase maternal investment, whereas maternal imprints offset this increase (Haig 2004). In plants there is also evidence that imprinting functions to suppress the transposition of TEs (Kohler & Weinhofer-Molisch 2009). Genomic conflict can clearly contribute importantly to the pattern of expression of alleles at a single locus.

In the context of epistasis, the most widespread form is sex-specific differences in the expression level of genes. For example, in mice at least 10,000 genes (most of which are autosomal) have sex-specific differences in gene expression within somatic tissues (Yang et al. 2006). Per tissue, numbers of transcripts with sexually dimorphic expression ranged from a low of 6% in brain to 35% in liver. Because the only genetic difference between males and females is the presence of the Y chromosome and the number of X chromosomes, there must be extensive epistasis between one or more genes on the sex chromosomes and thousands of autosomal genes. Assuming that much of the widespread sex differences in gene expression that we see today is adaptive—and represents the resolution of past intralocus sexual conflict—an understanding of such extensive epistasis requires an appreciation of the concept of intralocus sexual conflict.

Males and females are selected to do fundamentally different things. Males reproduce via sperm, and all the phenotypic traits that facilitate their sperm's transfer to, and use by, females. Females reproduce via eggs, and all the phenotypes that facilitate the production, fertilization, and survival of their eggs. This sexual dichotomy in reproductive function generates a genetic bipolarity: The same genes must code for different phenotypes (sometimes radically so, as in the case of testis versus ovary) when expressed in the two different sexual environments. The extent of this discordance was documented when the same random, genome-wide sets of genes were cloned and then expressed in male and female *D. melanogaster* (Chippindale et al. 2001). During the larval stage, when the sexes are similarly selected for growth and survival, there was a strong positive correlation for fitness among a group of 40 cloned genomes. But in the adult stage, where gender roles diverge, there was a strong negative correlation for fitness. Recent genome-wide gene expression studies indicate that the identity of gender-biased genes (with sex differences in expression) changes rapidly between closely related species (reviewed by Ellegren & Parsch 2007). These studies indicate that epistasis between genes on the sex chromosomes and thousands of autosomal genes is continually evolving, generating new gene-by-gene interactions. An understanding of the widespread epistasis associated with sex-specific gene expression requires an appreciation of the logic of intralocus sexual conflict.

Chromosomal Structure

The gross anatomy of eukaryotic chromosomes has three major forms: acrocentric, metacentric, and telocentric. Historically, most introductory texts provide no explanation for why more than one form exists; neither do they explain why the prevalence of the three types varies among taxa. We now know that the gross morphology of chromosomes influences their propensity to segregate to polar bodies during female meiosis, and the anatomical type that has an advantage (less likely

to segregate to a polar body) differs between taxonomic groups; this leads to differences in the prevalence of types among taxa (reviewed by Burt & Trivers 2006).

The centromere itself is of interest because it does not code for genes but represents a spindle attachment site for chromosomes during mitosis and meiosis. But if centromeres were merely a "handle," then why would they be among the fastest evolving parts of the genome (Malik & Henikoff 2009)? Recent evidence indicates that centromere sequences influence their propensity to migrate to polar bodies and are hence under directional selection to avoid this fate (reviewed by Malik & Bayes 2006). There is also evidence that mutant centromeres that successfully "cheat" during oogenesis sometimes lead to impaired function during spermatogenesis (reviewed by Elde et al. 2011). Such sexually antagonistic pleiotropy would result in both intralocus sexual conflict and interlocus conflict between the centromere driver and the rest of the genome when disruption to spermatogenesis is sufficiently strong. These examples demonstrate how the diversity of centromeric positions on chromosomes and their sequence among and within species can only be fully understood from the context of genomic conflict.

Sex Chromosomes

For brevity in what follows I will assume male heterogamety (XX females and XY males) with either no recombination between the X and Y or its restriction to a pseudoautosomal region (in which case X and Y will refer to their nonrecombining portions in males). Sex chromosomes contain many intrinsic transmission asymmetries. These include that (*a*) in males the Y is always transmitted from father to sons and the X from father to daughters; (*b*) the Y is transmitted exclusively through the patriline, causing it to be permanently heterozygous and three times less numerous than the X; and (*c*) the X recombines when in females but the male-limited Y is constantly nonrecombining. These transmission asymmetries essentially guarantee that sex chromosomes are especially prone to genomic conflict because they open up manifest opportunities for the evolution of unequal reproduction among genomic components. I only describe a few consequences of these asymmetries with respect to genomic conflict, but a fuller account is provided by Burt & Trivers (2006, see their chapter 3). Here I focus on the X chromosome and return to the Y chromosome in a later section.

The unique transmission and expression pattern of X-linked genes requires that the Y chromosome lacks homologous alleles. In humans there is now direct sequencing evidence that the Y's original complement of genes decayed over time (Skaletsky et al. 2003); i.e., the remains of many silenced and decaying homologs of X-linked genes can be identified on the extant Y chromosome. In *Drosophila*, TE insertions are especially common on chromosomal arms recently translocated to Y chromosomes, and their accumulation appears to have contributed importantly to the Y's decay (Steinemann & Steinemann 1997, Bachtrog 2003). Such TE-induced decay is predicted by intraindividual genomic conflict because suppressed recombination reduces the efficacy of selection against harm produced by TE insertions (Charlesworth & Langley 1989). Each time a Y-linked gene is silenced, it leads to nascent sex-linked gene expression and transmission, causing dosage imbalance in males between the X and autosomes (Straub & Becker 2007). Such nascent male-hemizygous loci on the X generate intralocus sexual conflict: Males benefit from new mutations that produce promoters and/or enhancers that increase the transcription rate of their *cis*-associated structural genes, whereas the status quo is favored in females (Wright & Mank 2012, Pessia et al. 2012a). Dosage compensation has evolved independently—and in manifestly different ways in different taxa—to resolve this intrinsic intralocus sexual conflict (reviewed by Dementyeva & Zakian 2010, Bachtrog et al. 2011). Studies of the decay of the Y chromosome, and

its consequences, illustrate how fundamental aspects of gene transmission and expression—sex linkage and dosage compensation—can only be fully understood in light of genomic conflict.

Another striking genetic pattern of the sex chromosomes is the distribution of genes coding for spermatogenesis and oogenesis. In some species, like the model organism *Caenorhabditis elegans*, the X is nearly devoid of spermatogenesis-specific genes, whereas oogenesis-specific genes are approximately randomly distributed between the X and autosomes (Reinke et al. 2000). This asymmetry is related to another sex chromosome asymmetry: meiotic sex chromosome inactivation (MSCI) in XX/XY species (Arico et al. 2011). In organisms as diverse as flies (Diptera), worms (Nematoda) and mammals (Mammalia), most genes on the sex chromosomes are silenced during male but not female gametogenesis (Bachtrog et al. 2011). One known mechanism hypothesized to contribute to MSCI is based on the fact that X-linked genes are hemizygous in males. During male meiosis and spermatogenesis, hemizygous X-linked genes are targeted by epigenetic modification pathways that silence unpaired genes. This silencing inactivates newly established parasitic TEs that transpose during meiosis and spermatogenesis (Slotkin & Martienssen 2007). Collateral silencing of nascent X-linked hemizygous genes generates selection for any genes necessary for spermatogenesis to be translocated from the X to the autosomes (where they avoid X-linked hemizygous expression) and hence their absence on extant sex chromosomes (Betran et al. 2002). However, this explanation for MSCI and the distribution of spermatogenesis-specific genes must be incomplete in the case of *C. elegans* because the X becomes a condensed, inactive "sex body" during meiosis in both XO males and XX hermaphrodites (Arico et al. 2011). In this case, MSCI and the near absence of spermatogenesis-specific genes on the X are more consistent with sex chromosome inactivation occurring during meiosis to prevent segregation distortion (Meiklejohn & Tao 2010) or zygotic drive of the sex chromosomes (Rice et al. 2008). Theory and data indicate that such selfish driving processes occur at elevated levels on the sex chromosomes compared to the autosomes (Hurst & Pomiankowski 1991, Burt & Trivers 2006). Irrespective of the relative importance of these alternative mechanisms (suppression of TEs, segregation distorters, and/or zygotic drivers), MSCI and the dearth of X-linked spermatogenesis genes provide additional examples of how genomic conflict has contributed importantly to sex chromosome form and function.

Recombination and Linkage Maps

Recombination and linkage maps are fundamental concepts in classical genetics because the recombination frequency between alleles at different genes provides the historic measure of how closely genes are positioned within the genome. Crossovers between homologous chromosomes are also a critical component of meiosis in the context of the prevention of aneuploid gametes. Genomic conflict plays a key role in understanding these fundamental features of recombination.

Map length can vary markedly between the sexes. For example, in humans the map length is 60% longer in females compared with males and this difference is expanded to over 800% in some salmonid fish, whereas the map length disparity is reversed to 30% shorter in male domestic sheep (reviewed by Hedrick 2007). In mice (Shifman et al. 2006) and humans (Fledel-Alon et al. 2011), both the genetic and phenotypic correlations between recombination rate in males and females are surprisingly weak despite substantial heritable genetic variation within each sex. In addition, the location of recombination hot spots can be markedly different between close relatives (reviewed by Coop & Przeworski 2007). These observations indicate that recombination is evolving rapidly and that there is sex-specific regulation of its rate. If recombination were simply a conserved mechanism to shuffle sperm and egg haplotypes and insure against nondisjunction of chromosomes during meiosis, we would not expect such heterogeneity between the sexes nor among closely related

species. However, we would expect such differences in regional recombination rates if they were evolving rapidly, and in a sex-specific manner, due to genomic conflict.

Studies of mutations affecting the recombination machinery have shown markedly different phenotypes in meiotic prophase of males compared with females (reviewed by Hunt & Hassold 2002). This observation demonstrates the substantial differences in the molecular environment influencing recombination in males and females and hence a rationale for the low correlation for recombination rate between the sexes. Although testis and ovary are both considered to be sexually dimorphic forms of the same organ (i.e., the gonad), they produce radically different end-products: sperm and eggs. The need to produce markedly dimorphic gametes by the same organ generated intense intralocus sexual conflict in ancestral plants and animals. Resolution of this intralocus sexual conflict has led to the gross phenotypic differences we see in extant testes and ovaries, including strong sexual dimorphism at the molecular level and, as an incidental by-product, low correspondence in map length between the sexes. There may also be directional selection for sexual dimorphism in map length between the sexes. For example, genomic conflict in the context of meiotic drive predicts the evolution of sex differences in recombination rate, especially where it is most pronounced, i.e., in centromere-proximate regions of chromosomes (e.g., Haig 2010, Brandvain & Coop 2012). Genomic conflict provides key insights into the ultimate causation of sex-specific differences in map length.

In some organisms as diverse as mammals and yeast, most recombination occurs in localized regions called recombinational hot spots (reviewed by Petes 2001). The low correspondence between the location of hot spots in humans and chimps demonstrates that hot spots can evolve rapidly (reviewed by Coop & Przeworski 2007). This rapid divergence between closely related species is predicted by genomic conflict that underlies the phenomenon of biased gene conversion (Nicolas et al. 1989, Boulton et al. 1997). "Hotter" sequences, which are more prone to double-strand cuts by the recombinational machinery, have their sequences replaced by those of less frequently cut "colder" alleles. The sequence replacement that occurs in hot spots is a consequence of double-strand digestion of DNA flanking the cut site of the hotter allele, followed by replacement of the digested DNA with the sequence from the colder uncut allele; this is a form of meiotic drive at the molecular level or "molecular drive" (Dover 1982). This fundamental feature of recombination—cut, digest, and replace—essentially guarantees that recombinational hot spots will be unstable across time due to a disadvantage in genomic conflict; alleles more prone to cutting have a molecular drive disadvantage, and this is a pattern that was recently confirmed empirically (Myers et al. 2010).

Although there may be multiple causes contributing to the sex specificity of recombination rate and the instability of recombinational hot spots across time, genomic conflict—in the forms of intralocus sexual conflict, molecular drive, and meiotic drive—clearly plays an important role in these fundamental components of the recombination process.

Structure and Replication of DNA

One of the fundamental aspects of DNA's structure and replication is its leading/lagging strand modes of replication. The ends of linear chromosomes cannot be replicated via the lagging strand mode, and some form of compensation is required to replicate these regions to prevent telomere shortening at each mitotic division. In the Diptera (including flies and about 10% of all animal species), the replication of telomeres is accomplished by a group of three domesticated TEs (Mason et al. 2011). By retrotransposing new elements into the telomeric region prior to cell division, telomere shortening is compensated. Although species like mammals use native telomerase to lengthen telomeres at each mitotic cell division, the symbiotic relationships that have evolved

between Dipterans and three of their intragenomic parasites to solve this problem underscore the importance of genomic conflict in understanding the replication of DNA in a major group of the animal kingdom.

DNA Repair

The spectrum of DNA repair systems is surprisingly diverse, owing in part to the diverse ways in which DNA can be damaged. One reason that genomic conflict is integral to understanding the form and function of DNA repair mechanisms is that many genomic parasites (e.g., many DNA transposons) rely on their hosts' DNA repair machinery for their replication. As a consequence, to understand the design of the DNA repair machinery, one must consider both its role in the repair of DNA damage and simultaneously its role in stemming the spread of harmful genomic parasites.

Another critical feature of DNA repair is a consequence of intrinsic biases. During heteroduplex formation of meiosis in yeast, biased gene conversion weakly favors GC-alleles over AT-alleles (reviewed by Duret & Galtier 2009). Indirect evidence indicates a similar bias in mammals and other diverse taxa (Pessia et al. 2012b). A candidate mechanism for the repair bias comes from studies of mitotic mismatch repair in which CT mismatches are usually repaired to GC—presumably in response to the relatively high incidence of deamination of methylated cytosine bases to form thymines (Jones et al. 1987). If this mitotic base excision repair system contributes to at least some of the mismatch repair in mitosis of the germ line, or during meiosis itself, it will bias gene conversion away from AT sites and toward GC sites. Irrespective of the underlying mechanism, bias in gene conversion represents a form of molecular drive and hence a form of genomic conflict. Isochores of GC-rich chromatin are a recurrent observed phenomenon across a wide diversity of species, and genomic conflict via biased gene conversion is critical to understanding this fundamental structure (Duret & Galtier 2009).

The Central Dogma

A unifying paradigm of molecular genetics originally proposed by Crick (1958, 1970) is that the flow of genetic information is unidirectional: DNA → RNA → protein. Many biological functions follow this paradigm, but we now know that many do not and that genomic conflict plays a key role in many such "heresies." For example, retrotransposons make up as much as one-third of the genome of some mammals, yet these abundant genes break the central dogma via reverse transcription in which RNA codes for the information in DNA. Another deviation from the central dogma includes gene regulation via the siRNA, miRNA, and piRNA pathways in which part of the flow of information is RNA → DNA. All of these pathways appear to have evolved from antiviral/antiretrotransposon defenses (Bagasra & Prilliman 2004); hence, an understanding of their form and function requires an appreciation and understanding of the genomic conflict that generated them.

Gene Fine Structure

One of the most surprising discoveries in the field of molecular genetics was the finding in the early 1970s that eukaryotic genes are usually interrupted by one or more noncoding sequences called introns. This discovery led to the "genes in pieces" paradigm (Gilbert 1978). The ramifications of introns to the field of genetics are substantial. For example, alternative splice sites can dramatically increase the information content of a single genomic region, and long introns can code

for important regulatory information. But our understanding of the birth and death processes of these fundamental genetic units has been poorly understood until recently. In most lineages, the presence/absence and splice sites of specific introns are highly conserved across tens of millions of years (Roy & Gilbert 2006, Stajich et al. 2007). Yet among distant lineages the numbers and positions of introns can vary dramatically, and in some species the presence/absence and splice sites of introns are currently segregating within single populations (Li et al. 2009).

Although there are many mechanisms that can generate new introns (Roy & Irimia 2012), two recent studies demonstrate that bursts of thousands of new introns can spread within genomes over geologically short periods of time due to one of two families of proliferating elements termed introners (Worden et al. 2009) and introner-like elements (van der Burgt et al. 2012) that are removed from transcripts as if they were introns because they contain the canonical spliceosomal splicing motifs. These de novo introns are found in unrelated genes located across the genome. Work on another group of nascent introns indicates that they are intrinsically deleterious and accumulate when random genetic drift overpowers selection (Li et al. 2009). Collectively these studies indicate that many, probably most, introns have accumulated as genomic parasites that take advantage of the extant spliceosomal machinery to proliferate. Thus a basic understanding of another fundamental concept in modern genetics—genes in pieces—requires an appreciation of genomic conflict.

Gene Regulation

In eukaryotes, genes are regulated by *trans*-acting transcription factors as well as *cis*-acting enhancers, promoters, and epigenetic modifications of these *cis* elements. Understanding the creation, diversity, form, and function of these regulatory elements requires an understanding of genomic conflict. For example, recent evidence from humans indicates that TEs make up nearly half of the genome (Lander et al. 2001). Nearly all of these TEs are now inactive, but their decaying carcasses have provided substantial opportunity for the creation of new regulatory elements. Unlike random sequences of DNA, TEs are enriched with regulatory elements that, with small mutational modification, can create new *cis*-acting regulatory elements for their host. A recent survey found that about one-third of all binding sites for a group of five transcription factors (ESR1, TP53, POU5F1, SOX2, and CTCF) were embedded in TEs (Bourque 2009). Another study found that at least 1,500 genes in humans initiate transcription from promoters derived from TE sequences and obtain tissue specificity via differential epigenetic modification of TE-derived sequences (Huda et al. 2011). Similar statistical analyses indicate that many enhancers originate as domesticated TE sequences (Bourque 2009). These and similar studies demonstrate that a high proportion of eukaryotic *cis*-regulatory elements are created from the decaying carcasses of TEs. These examples illustrate how an understanding of the creation, function, and diversity of gene regulation mechanisms requires an appreciation of how what began as genomic conflict between host genomes and their genomic parasites can ultimately lead to complex networks of gene regulation.

Gene and Chromosomal Mutation

There are many ways to change the sequence of DNA, but intragenomic conflict unquestionably contributes importantly to this fundamental genetic process. For example, in *Drosophila* there is substantial evidence that TEs are common parasites that make up about 12% of the genome (Charlesworth & Langley 1989, Kidwell 2002). The importance of TEs in the mutation process is demonstrated by the fact that TE insertions account for about 80% of the cataloged visible point

mutations in *D. melanogaster* (Ashburner et al. 2005), and they also contribute substantially to genetic variation for quantitative traits (reviewed by Kidwell & Lisch 1997). In addition, ectopic exchange between TEs contributes importantly to gross structural mutations of chromosomes, such as inversions and translocations (Charlesworth & Langley 1989). The substantial role of TEs, and hence genomic conflict, in the mutational process is clearly evident.

Extranuclear Genes

Eukaryotic genomes are composed of both nuclear and cytoplasmic components. Mitochondria and chloroplasts are examples of cytoplasmic components derived from ancient symbioses with prokaryotes, whereas bacteria like *Rickettsia*, *Wolbachia*, and *Spiroplasma* are examples of more recently attained symbionts. In some species, like *Wolbachia*, the symbiosis can be obligate, such that the eukaryotic host (and all of its nuclear genes) dies when the symbiont is removed with antibiotics (reviewed by Charlat et al. 2003). Cytoplasmic symbionts are usually not transferred to zygotes via the sperm or pollen, and as a consequence, the nuclear/cytoplasmic structure of many eukaryotic genomes guarantees high opportunity for intense intraindividual genomic conflict. Because of the fundamental nuclear/cytoplasmic genome structure of most eukaryotes, an understanding of cytonuclear genomic conflict is crucial to understanding their genetic organization.

Cytonuclear conflict can be both active and passive. The passive form occurs because males are transmission dead-ends for cytoplasmic genes and therefore selection for male-function cannot be manifest unless male relatives are somehow necessary for a female's survival, as occurs, for example, in species with sib-mating (Wade 2009). As a consequence, mitochondrial and chloroplast genes are favored if they benefit female function irrespective of any harmful effect to males; i.e., they will be favored by natural selection even if they cause elevated mortality or sterility in males. This evolutionary asymmetry is melodramatically called the mother's curse (Gemmell et al. 2004). Some of the most convincing direct evidence for the mother's curse has only accrued recently. Innocenti et al. (2011) collected mitochondria from *D. melanogaster* populations taken from different parts of the globe and recombined them into the same nuclear genomic background. They next measured genome-wide gene expression profiles in males and females. In females, the different mitochondrial genomes had no obvious phenotypic effects and nearly no effect on gene expression profiles with only 0.6% of nuclear genes affected (7 genes), which is consistent with the idea that mitochondria evolve in a manner that is harmonious with gene expression in females. But in males, swapping mitochondria resulted in a shift in transcript expression in 1,172 genes (about 9% of the nuclear genes). Most of these genes were male-biased in expression, with "enrichment hot spots" found in the testes and accessory gland (that produces seminal fluid). In one case the mitochondrial swap was so disruptive to gene expression that it led to complete male sterility.

Active cytonuclear genomic conflict has been documented in a wide diversity of hermaphroditic flowering plants, including at least 140 species distributed among 47 genera and 20 families (Laser & Lersten 1972; see also Burt & Trivers 2006, their chapter five). In these species the mitochondria are only transmitted through ovules and not through pollen. Correspondingly, mitochondrial genotypes have repeatedly evolved that cause pollen production to be aborted, presumably freeing up more resources for ovule production, through which the mitochondria reproduce. Mitochondrial pollen killers are only episodically active across geological time because nuclear suppressors evolve to silence them (Kaul 1988). As a consequence, they are usually completely hidden in nature (and thereby unappreciated as important genomic components) and only uncovered in crosses between closely related species that separate pollen-killing mitochondrial genotypes from their suppressors (Kaul 1988). Available data indicate that such repressors reestablish parity between male and female reproductive function and contribute to an "arms race" between pollen-killing

mitochondria and their suppressors (reviewed by Burt & Trivers 2006). Interestingly, there are no reported cases of sperm- or son-killing mitochondria in animals (Burt & Trivers 2006). This difference between plants and animals may simply reflect the much smaller number of protein-coding genes (and hence lower evolutionary potential) found on the extant mitochondria of animals (12–13 in animals versus 24–40 in plants; reviewed by Burt & Trivers 2006) because newer bacterial endosymbionts (residing in animals) with larger genomes clearly can and do evolve to harm sons and manipulate sperm, as described below.

A second and common form of active cytonuclear conflict occurs between more recently established cytoplasmic endosymbionts and the nuclear genome of their hosts. For example, *Wolbachia* is a surprisingly common endosymbiont in invertebrates, infecting about 65% of all insects (Hilgenboecker et al. 2008). In some cases the symbiosis is obligate; e.g., *Drosophila willistoni* die when cured of the bacteria with antibiotics (Miller et al. 2010). Like mitochondria, *Wolbachia* are only propagated through the matriline because they are removed along with most of the cytoplasm during sperm maturation. Accordingly, *Wolbachia* have evolved several phenotypes that kill sons, feminize them, or convert them into "smart bombs" that kill all offspring that do not carry the same strain of *Wolbachia* (Charlat et al. 2003). As occurs in the case of plant mitochondria, nuclear genes evolve to silence or ameliorate the harmful phenotypes that *Wolbachia* has evolved, setting the stage for a protracted arms race between the endosymbiont and nuclear repressors coded by the host genome.

Sex-Limited Nuclear Genes

For brevity in the remainder of this section, I focus on Y chromosomes of males, but similar logic applies to the W chromosomes of females. Because the Y is transmitted exclusively through the patriline, it has the same sex-limited transmission characteristics as cytoplasmic genes, but with the sexes reversed. The Y is therefore expected to evolve to harm the noncarrier sex of offspring, as is done by *Wolbachia* and *Spiroplasma* of animals (Rice et al. 2008) and/or the noncarrier X-bearing gamete (Hamilton 1969). Why then do we not have the numerous empirical examples of selfish Y chromosomes that harm noncarriers as we do for the X chromosomes?

The simplest answer to the above question is that the Y in humans and in most model organisms has degenerated to the point that it has too few genes to code the complex traits needed to produce a driving phenotype. However, recent evidence from *D. melanogaster* indicates that even though the Y is a coding dwarf (with only 13 known structural genes, all with testis-limited expression), it is a regulatory giant (Sackton et al. 2011 and references therein). In this succession of studies, many hundreds of X-linked and autosomal genes had their transcription rate changed in males depending on the identity of the Y chromosomes that they carried, which were derived from different populations or species. The Y also influences many quantitative traits in mice (Nelson et al. 2010). There is also recent evidence in *D. melanogaster* that the paternal Y influences the survival of noncarrier daughters (Friberg et al. 2012), and in mice the paternal Y was found to *trans*-generationally influence a wide diversity of traits in a father's daughters (Nelson et al. 2010). Clearly the Y retains at least some regulatory potential to code for genomic conflict.

In the mosquito (*Culex pipiens*, a species where the Y is still gene-rich), there is a clear example of a Y chromosome causing segregation distortion (Sweeny & Barr 1978). However, until recently I was unable to find even a single well-documented example of strong segregation distortion coded by a highly degenerated Y chromosome. Cocquet et al. (2012) discovered multicopy genes on the X (*Slx* and *Slxl1*) and the Y (*Sly*) that interact antagonistically and influence segregation distortion of sex chromosomes in mice. Using RNAi to knock down these Y-linked genes and/or X-linked genes, sex ratio was strongly influenced. Knocking down (*a*) the Y-linked *Sly* genes led to X-linked

gametic drive and a female-biased sex ratio, (*b*) the X-linked genes led to Y-linked gametic drive and a male-biased sex ratio, and lastly, (*c*) both the Y-linked and X-linked genes led to an equal sex ratio. The SLY and SLX/SSXL1 proteins were shown to strongly influence epigenetic marks controlling postmeiotic gene expression on both the sex chromosomes and the autosomes, and also to compete for the same regulatory binding sites on both autosomal and X-linked loci expressed postmeiotically during spermatogenesis. This study represents proof of process that despite its low number of coding genes, the Y chromosome may contribute to genomic conflict—but this effect is only expressed episodically when new mutations break the stalemate between drivers and their suppressors. Another reason that numerous examples of Y-linked gametic drivers may be rare in the literature is because, unlike the X-linked gametic drivers, the requisite conditions for stable Y-linked polymorphisms for gametic drive are highly restrictive (Clark 1987); hence, Y-linked drivers, though present, are expected to be hidden from view nearly all of the time unless uncovered by experimental RNAi knockdown or introgression of Y chromosomes between populations or species.

Just as endosymbionts like *Wolbachia* and *Spiroplasma* are selected to kill noncarrier sons, so too are Y chromosomes selected to kill daughters that do not carry them (Y-linked sexually antagonistic (SA)-zygotic drive, Rice et al. 2008). However, I know of no established examples of gene-poor Y chromosomes that kill daughters (neither do I know of any gene-poor animal mitochondria that presently kill sons). There is, however, preliminary evidence for a gene-rich X chromosome that kills sons in *D. simulans* (Friberg et al. 2011) and one intriguing report of a human X-linked paternal grandson-killer (Fox et al. 2010). The evolutionary logic behind cytoplasmic bacteria that kill sons, and the many established cases of this phenomenon, suggests that both the mitochondria of animals and Y chromosomes may have killed the noncarrier sex of offspring before they degenerated to their present gene-depleted state. Gene-depleted mitochondria and Y chromosomes may presently produce only modest, quantitative effects on the survival of noncarrier sex that are difficult to statistically demonstrate and are easily confused with polygenic sex-specific mortality. Until (*a*) the requisite interspecific introgressions of Y chromosomes are carried out, (*b*) recombinant inbred lines are constructed between isolated populations of the same or closely related species, or (*c*) RNAi knockdown of candidate Y-linked genes is done (as in the mouse example, Cocquet et al. 2012), the role of the Y in harming noncarrier daughters remains theoretical. Nonetheless, given the widespread evolution of mitochondrial pollen killers, son-killing by cytoplasmic endosymbionts, and the established potential for Y-linked *trans*-generational effects, it seems inevitable that at least some cases of Y-coded daughter-killing/harming will be uncovered in the future.

Developmental Genetics

A fundamental question in developmental genetics is how a single genome can code simultaneously for two functionally divergent phenotypes: males and females. The developmental decision to initiate a male versus female developmental pathway must have first evolved hundreds of millions of years ago and remained essentially invariant in most lineages. Such an ancient and invariant developmental decision would be expected to lead to a highly conserved developmental pathway, yet it is remarkably diverse in nature, even between closely related species (Bull 1983). For example, in some fish, different populations of the same species are XX/XY, others ZZ/ZW, and yet others are polymorphic for both systems simultaneously (Bull 1983).

Intragenomic conflict appears to contribute importantly to the diversity of sex determination pathways. Recent theory in evolutionary genetics predicts that genetic hitchhiking between sexually antagonistic alleles and linked mutations coding for alternative switches in the

sex-determination regulatory cascade is a common cause for related species having different sex determination systems—this is supported by many empirical examples in fish (van Doorn & Kirkpatrick 2007). Another form of intragenomic conflict—meiotic drive and/or segregation distortion—has also been proposed as a causative agent contributing to change in the sex-determining mechanism among closely related species (Kozielska et al. 2009). Supporting evidence for this mechanism comes from a wide diversity of organisms, including the wood lemming (*Myopus schisticolor*), mole (*Talpa occidentalis*), creeping vole (*Microtus oregoni)*, sciarid fly (*Sciara coprophila*), housefly (*Musca domestica*), and scale insects (*Neococcoidea*) (summarized by Kozielska et al. 2009).

The male intromittent organ is a pivotal end-point of the sex-determination developmental pathway. Given its conserved function, one would reasonably expect this organ to be highly conserved among closely related species. But in contrast to this expectation, the intromittent organ is among the most rapidly diverging traits among all of the phenotypic components of an organism (Eberhard 1996). Genomic conflict, in the forms of interlocus sexual conflict and interlocus contest evolution, predicts the rapid evolution of this structure (Parker 1979, Rice & Holland 1997, Arnqvist & Rowe 2002). For example, in the Muscovy duck (*Cairina moschata*) there is an enigmatic asymmetry between the geometry of the penis (rotated clockwise) and the vagina (rotated counterclockwise). Recent experiments demonstrate that this noncongruence permits females to better resist forced copulations by males (Brennan et al. 2010). Numerous other examples of such an arms race between male and female genitalia are summarized by Arnqvist & Rowe (2005).

Population/Evolutionary Genetics

A fundamental component of evolutionary genetics is the process of speciation. Postzygotic reproductive isolation between species develops due to the accumulation of Muller-Dobzhansky (MZ) incompatibilities that kill or sterilize hybrids. Recent genetic work has focused on the genetic mechanisms that contribute to the development of MZ incompatibilities. Although the number of established "speciation genes" is still small, there is already clear evidence that genomic conflict, in the form of segregation distorters, is an important contributor (summarized by McDermott & Noor 2010). These recent discoveries demonstrate that an understanding of one of the pivotal components of evolution, the genetic basis of speciation, requires an appreciation and knowledge of intragenomic conflict.

Natural selection is one of the four deterministic forces leading to gene frequency change within a population and hence the process of evolution. It is defined as the process by which organisms with traits that best match the demands of their environment produce more offspring and thereby contribute more of their genes to the next generation. Natural selection is traditionally decomposed into sexual selection and all other forms of selection (which I call survival selection). Sexual selection occurs due to differential access to fertilization opportunities, mediated by mating preferences—usually by females for males—and also via contests between males to mate with females or between sperm to fertilize eggs in multiply mated females. Survival selection includes all other forms of natural selection that influence survival and fertility. Darwin separated sexual from natural selection because the former type of selection counterintuitively leads to the evolution of traits that reduce survival—so long as this loss is more than compensated for by increased mating and fertilization success.

Missing in the dichotomy of sexual versus survival selection is a category of selection due to genomic conflict. Antagonistic interactions within the genome of a single species are even more counterintuitive relative to the concept of "survival of the fittest" than are traits like a survival-reducing

peacock's tail that motivated Darwin to develop the concept of sexual selection. For this reason, I conclude that a new category of natural selection is justified that describes evolution in response to antagonistic interactions between components of the genome of a single species. Genomic conflict selection, or more compactly GenCon-selection, would be a suitable name for this type of selection.

Comparative Genomics

One of the hallmarks of comparative genomics is the structural change that accrues between species: Gene families expand and contract, new genes are formed from formerly noncoding sequences, and chromosomal parts are inverted and exchanged. Genomic conflict—in the form of parasitic TEs—contributes importantly to the ectopic recombination that underlies major exchanges between chromosomes, inversions within chromosomes, and the expansion of gene families to new locations. Promoters and enhancers derived from TEs also contribute to changes in tissue-specific gene expression profiles between species as well as in the recruitment of de novo genes that fortuitously become transcriptionally controlled by *cis*-acting regulatory elements of TEs. The importance of intragenomic conflict to genome-scale changes is so self-evident that I will not belabor the point here.

FINAL REMARKS

In this review, I have tried to show how all of the major components of the field of genetics are substantially influenced by genomic conflict. Space constraints prevented a fuller accounting of this relationship, but illustrative examples were provided for all of the major subfields of eukaryotic genetics. Of course, the word "nothing" in my title may lead some to conclude that it is a hyperbolic exaggeration. However, the same could be said about Dobzhansky's famous article containing the same word (*Nothing in Biology Makes Sense Except in Light of Evolution*). An understanding of many of the foundational components of biology (e.g., energy metabolism or the structure and replication of DNA) depend more on physical chemical concepts, like Michaelis-Menten enzyme kinetics and the unique molecular geometry created by sp^3 hybridization of carbon atoms, than on the process of organic evolution. Nonetheless, all of the more complex biological features found in nature are influenced by evolution in an ultimate sense because evolution is the process that built them. By similar logic, all of the fundamental concepts of genetics are influenced by genomic conflict because all genomes contain intrinsic internal conflicts owing to the fact that some of their parts can reproduce at the expense of others.

Our original, and indirect, view of the genome from the early twentieth century was that of a hereditary blueprint consisting of a network of congruent instructions (genes) and little or nothing else. As advances in technology have revealed more of the actual structure of the genome, this view is being replaced by that of a hereditary ecosystem. From this perspective, many genomic parts interact harmoniously like mutualistic symbionts (e.g., genes coding for hormones and their receptors or for different parts of integrated physiological and developmental networks). However, such mutualistically coevolving parts are not alone. Genomic parts can also interact like exploitative competitors (e.g., meiotic drivers, SA alleles, and feminizing cytoplasmic endosymbionts), mortality-inducing interference competitors (segregation distorters, zygotic drivers, pollen-killing mitochondria, son-harming mitochondria, and endosymbiotic genomes—some of which are obligate—that kill nontransmitting daughters and/or sons), parasites (most TEs and nonessential B chromosomes), and predators (e.g., homing endonucleases and those TEs causing insertional inactivation). Gene duplications, many of which are transposon mediated, provide a parallel to the process of speciation. Even the process of extinction via consumer overexploitation

has parallels in the genome (e.g., the insertional inactivation of many Y- and W-linked genes due to uncontrolled transposon accumulation in response to a reduced efficacy of selection on nonrecombining sex chromosomes). Just as much of the energy and nutrients within ecosystems can reside in dead and decaying biomass (though some is recycled back into the living ecosystem), so too does much of the genome of many species consist of dead and decaying TEs and duplicated genes, some of which are recycled into new genetic functions (e.g., TE-derived regulatory elements, TE-mediated intron expansions and reactivated pseudogenes with neofunctionalization). A full understanding of essentially all aspects of genetics must encompass the action and diverse consequences of genomic conflict because, unlike a harmoniously integrated blueprint, all genomes contain intrinsically conflicted parts that coevolve antagonistically in a hereditary ecosystem.

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LITERATURE CITED

Arico JK, Katz DJ, van der Vlag J, Kelly WG. 2011. Epigenetic patterns maintained in early *Caenorhabditis elegans* embryos can be established by gene activity in the parental germ cells. *PLoS Genet.* 7:e1001391

Arnqvist G, Rowe L. 2002. Antagonistic coevolution between the sexes in a group of insects. *Nature* 415:787–89

Arnqvist G, Rowe L. 2005. *Sexual Conflict*. Princeton, NJ: Princeton Univ. Press

Ashburner M, Golic K, Hawley R. 2005. *Drosophila: A Laboratory Handbook.* Cold Spring Harbor, NY: Cold Spring Harb. Lab. Press

Aziz RK, Breitbart M, Edwards RA. 2010. Transposases are the most abundant, most ubiquitous genes in nature. *Nucleic Acids Res.* 38:4207–17

Bachtrog D. 2003. Accumulation of Spock and Worf, two novel non-LTR retrotransposons, on the neo-Y chromosome of *Drosophila miranda*. *Mol. Biol. Evol.* 20:173–81

Bachtrog D, Kirkpatrick M, Mank JE, McDaniel SF, Pires JC, et al. 2011. Are all sex chromosomes created equal? *Trends Genet.* 27:350–57

Bagasra O, Prilliman KR. 2004. RNA interference: the molecular immune system. *J. Mol. Histol.* 35:545–53

Betran E, Thornton K, Long M. 2002. Retroposed new genes out of the X in *Drosophila*. *Genome Res.* 12:1854–59

Boulton A, Myers RS, Redfield RJ. 1997. The hotspot conversion paradox and the evolution of meiotic recombination. *Proc. Natl. Acad. Sci. USA* 94:8058–63

Bourque G. 2009. Transposable elements in gene regulation and in the evolution of vertebrate genomes. *Curr. Opin. Genet. Dev.* 19:607–12

Brandvain Y, Coop G. 2012. Scrambling eggs: meiotic drive and the evolution of female recombination rates. *Genetics* 190:709–23

Brennan PLR, Clark CJ, Prum RO. 2010. Explosive eversion and functional morphology of the duck penis supports sexual conflict in waterfowl genitalia. *Proc. R. Soc. B* 277:1309–14

Buckler ES, Phelps-Durr TL, Buckler CSK, Dawe RK, Doebley JF, Holtsford TP. 1999. Meiotic drive of chromosomal knobs reshaped the maize genome. *Genetics* 153:415–26

Bull JJ. 1983. *Evolution of Sex Determining Mechanisms*. Menlo Park, CA: Benjamin/Cummings

Burt A, Trivers R. 2006. *Genes in Conflict: the Biology of Selfish Genetic Elements.* Cambridge, MA: Belknap

Charlat S, Hurst GDD, Mercot H. 2003. Evolutionary consequences of *Wolbachia* infections. *Trends Genet.* 19:217–23

Charlesworth B, Langley CH. 1989. The population genetics of *Drosophila* transposable elements. *Annu. Rev. Genet.* 23:251–87
Chippindale AK, Gibson JR, Rice WR. 2001. Negative genetic correlation for adult fitness between sexes reveals ontogenetic conflict in *Drosophila*. *Proc. Natl. Acad. Sci. USA* 98:1671–75
Clark AG. 1987. Natural selection and Y-linked polymorphism. *Genetics* 115:569–77
Cocquet J, Ellis PJI, Mahadevaiah SK, Affara NA, Vaiman D, Burgoyne PS. 2012. A genetic basis for a postmeiotic X versus Y chromosome intragenomic conflict in the mouse. *PLoS Genet.* 8:e1002900
Coop G, Przeworski M. 2007. An evolutionary view of human recombination. *Nat. Rev. Genet.* 8:23–34
Crick FH. 1958. On protein synthesis. *Symp. Soc. Exp. Biol.* 12:139–63
Crick FH. 1970. Central dogma of molecular biology. *Nature* 227:561–63
Dean NL, Loredo-Osti JC, Fujiwara TM, Morgan K, Tan SL, et al. 2006. Transmission ratio distortion in the myotonic dystrophy locus in human preimplantation embryos. *Eur. J. Hum. Genet.* 14:299–306
Dementyeva EV, Zakian SM. 2010. Dosage compensation of sex chromosome genes in eukaryotes. *Acta Nat.* 2:36–43
Dermitzakis ET, Masly JP, Waldrip HM, Clark AG. 2000. Non-Mendelian segregation of sex chromosomes in heterospecific *Drosophila* males. *Genetics* 154:687–94
Dobzhansky T. 1973. Nothing in biology makes sense except in the light of evolution. *Am. Biol. Teach.* 35:125–29
Dover G. 1982. A molecular drive through evolution. *BioScience* 32:526–33
Duret L, Galtier N. 2009. Biased gene conversion and the evolution of mammalian genomic landscapes. *Annu. Rev. Genomics Hum. Genet.* 10:285–311
Eberhard W. 1996. *Female Control: Sexual Selection by Cryptic Female Choice*. Princeton, NJ: Princeton Univ. Press
Elde NC, Roach KC, Yao MC, Malik HS. 2011. Absence of positive selection on centromeric histones in *Tetrahymena* suggests unsuppressed centromere-drive in lineages lacking male meiosis. *J. Mol. Evol.* 72:510–20
Ellegren H, Parsch J. 2007. The evolution of sex-biased genes and sex-biased gene expression. *Nat. Rev. Genet.* 8:689–98
Fledel-Alon A, Leffler EM, Guan Y, Stephens M, Coop G, Przeworski M. 2011. Variation in human recombination rates and its genetic determinants. *PLoS ONE* 6:e20321
Fox M, Sear R, Beise J, Ragsdale G, Voland E, Knapp LA. 2010. Grandma plays favourites: X-chromosome relatedness and sex-specific childhood mortality. *Proc. R. Soc. B* 277:567–73
Friberg U, Stewart AD, Rice WR. 2011. Empirical evidence for son-killing X chromosomes and the operation of SA-zygotic drive. *PLoS ONE* 6:e23508
Friberg U, Stewart AD, Rice WR. 2012. X- and Y-chromosome linked paternal effects on a life-history trait. *Biol. Lett.* 8:71–73
Gemmell NJ, Metcalf VJ, Allendorf FW. 2004. Mother's curse: the effect of mtDNA on individual fitness and population viability. *Trends Ecol. Evol.* 19:238–44
Gilbert W. 1978. Why genes in pieces? *Nature* 271:501
Haig D. 1993. Genetic conflicts in human pregnancy. *Q. Rev. Biol.* 68:495–532
Haig D. 2004. Genomic imprinting and kinship: how good is the evidence? *Annu. Rev. Genet.* 38:553–85
Haig D. 2010. Games in tetrads: segregation, recombination, and meiotic drive. *Am. Nat.* 176:404–13
Hamilton WD. 1967. Extraordinary sex ratios. *Science* 156:477–88
Hedrick PW. 2007. Sex: differences in mutation, recombination, selection, gene flow, and genetic drift. *Evolution* 61:2750–71
Hilgenboecker K, Hammerstein P, Schlattmann P, Telschow A, Werren JH. 2008. How many species are infected with *Wolbachia*? A statistical analysis of current data. *FEMS Microbiol. Lett.* 281:215–20
Huda A, Bowen NJ, Conley AB, Jordan IK. 2011. Epigenetic regulation of transposable element derived human gene promoters. *Gene* 475:39–48
Hunt PA, Hassold TJ. 2002. Sex matters in meiosis. *Sci. Signal.* 296:2181
Hurst GDD, Werren JH. 2001. The role of selfish genetic elements in eukaryotic evolution. *Nat. Rev. Genet.* 2:597–606

Hurst LD, Pomiankowski A. 1991. Causes of sex ratio bias may account for unisexual sterility in hybrids: a new explanation of Haldane's rule and related phenomena. *Genetics* 128:841–58
Huxley J. 1942. *Evolution: The Modern Synthesis*. London: Allen & Unwin
Innocenti P, Morrow EH, Dowling DK. 2011. Experimental evidence supports a sex-specific selective sieve in mitochondrial genome evolution. *Science* 332:845–48
Jones M, Wagner R, Radman M. 1987. Repair of a mismatch is influenced by the base composition of the surrounding nucleotide sequence. *Genetics* 115:605–10
Kaul MLH. 1988. *Male Sterility in Higher Plants*. Berlin: Springer-Verlag
Kidwell MG. 2002. Transposable elements and the evolution of genome size in eukaryotes. *Genetica* 115:49–63
Kidwell MG, Lisch D. 1997. Transposable elements as sources of variation in animals and plants. *Proc. Natl. Acad. Sci. USA* 94:7704–11
Kohler C, Weinhofer-Molisch I. 2009. Mechanisms and evolution of genomic imprinting in plants. *Heredity* 105:57–63
Kozielska M, Weissing FJ, Beukeboom LW, Pen I. 2009. Segregation distortion and the evolution of sex-determining mechanisms. *Heredity* 104:100–12
Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, et al. 2001. Initial sequencing and analysis of the human genome. *Nature* 409:860–921
Laser KD, Lersten NR. 1972. Anatomy and cytology of microsporogenesis in cytoplasmic male sterile angiosperms. *Bot. Rev.* 38:425–54
Li W, Tucker AE, Sung W, Thomas WK, Lynch M. 2009. Extensive, recent intron gains in *Daphnia* populations. *Science* 326:1260–62
Lynch M. 2007. *The Origins of Genome Architecture*. Sunderland, MA: Sinauer
Malik HS, Bayes JJ. 2006. Genetic conflicts during meiosis and the evolutionary origins of centromere complexity. *Biochem. Soc. Trans.* 34:569–73
Malik HS, Henikoff S. 2009. Major evolutionary transitions in centromere complexity. *Cell* 138:1067–82
Mason JM, Reddy HM, Frydrychova RC. 2011. Telomere maintenance in organisms without telomerase. In *DNA Replication—Current Advances*, ed. H Seligmann, pp. 323–46. Rijeka, Croatia: InTech
McClintock B. 1950. The origin and behavior of mutable loci in maize. *Proc. Natl. Acad. Sci. USA* 36:344–55
McDermott SR, Noor MAF. 2010. The role of meiotic drive in hybrid male sterility. *Philos. Trans. R. Soc. B* 365:1265–72
Meiklejohn CD, Tao Y. 2010. Genetic conflict and sex chromosome evolution. *Trends Ecol. Evol.* 25:215–23
Miller WJ, Ehrman L, Schneider D. 2010. Infectious speciation revisited: impact of symbiont-depletion on female fitness and mating behavior of *Drosophila paulistorum*. *PLoS Pathog.* 6:e1001214
Montchamp-Moreau C, Cazemajor M. 2002. Sex-ratio drive in *Drosophila simulans*: variation in segregation ratio of X chromosomes from a natural population. *Genetics* 162:1221–31
Morgan T, Sturtevant A, Muller H, Bridges C. 1915. *The Mechanism of Mendelian Inheritance*. New York: Holt
Myers S, Bowden R, Tumian A, Bontrop RE, Freeman C, et al. 2010. Drive against hotspot motifs in primates implicates the PRDM9 gene in meiotic recombination. *Science* 327:876–79
Nelson VR, Spiezio SH, Nadeau JH. 2010. Transgenerational genetic effects of the paternal Y chromosome on daughters' phenotypes. *Epigenomics* 2:513–21
Nicolas A, Treco D, Schultes NP, Szostak JW. 1989. An initiation site for meiotic gene conversion in the yeast *Saccharomyces cerevisiae*. *Nature* 338:35
Parker G. 1979. Sexual selection and sexual conflict. In *Sexual Selection and Reproductive Competition in Insects*, ed. MS Blum, NA Blum, pp. 123–66. New York: Academic
Pessia E, Makino T, Bailly-Bechet M, McLysaght A, Marais GAB. 2012a. Mammalian X chromosome inactivation evolved as a dosage-compensation mechanism for dosage-sensitive genes on the X chromosome. *Proc. Natl. Acad. Sci. USA* 109:5346–51
Pessia E, Popa A, Mousset S, Rezvoy C, Duret L, Marais GAB. 2012b. Evidence for widespread GC-biased gene conversion in eukaryotes. *Genome Biol. Evol.* 4:675–82
Petes TD. 2001. Meiotic recombination hot spots and cold spots. *Nat. Rev. Genet.* 2:360–69
Reinke V, Smith HE, Nance J , Wang J, Van Doren C, et al. 2000. A global profile of germline gene expression in *C. elegans*. *Mol. Cell* 6:605–16

Rice WR. 1984. Sex chromosomes and the evolution of sexual dimorphism. *Evolution* 38:735–42
Rice WR, Gavrilets S, Friberg U. 2008. Sexually antagonistic zygotic drive of the sex chromosomes. *PLoS Genet.* 4:e1000313
Rice WR, Holland B. 1997. The enemies within: intergenomic conflict, interlocus contest evolution (ICE), and the intraspecific Red Queen. *Behav. Ecol. Sociobiol.* 41:1–10
Roy SW, Gilbert W. 2006. The evolution of spliceosomal introns: patterns, puzzles and progress. *Nat. Rev. Genet.* 7:211–21
Roy SW, Irimia M. 2012. Genome evolution: Where do new introns come from? *Curr. Biol.* 22:R529–31
Sackton TB, Montenegro H, Hartl DL, Lemos B. 2011. Interspecific Y chromosome introgressions disrupt testis-specific gene expression and male reproductive phenotypes in *Drosophila*. *Proc. Natl. Acad. Sci. USA* 108:17046–51
Sandler L, Novitski E. 1957. Meiotic drive as an evolutionary force. *Am. Nat.* 91:105–10
Shifman S, Bell JT, Copley RR, Taylor MS, Williams RW, et al. 2006. A high-resolution single nucleotide polymorphism genetic map of the mouse genome. *PLoS Biol.* 4:e395
Skaletsky H, Kuroda-Kawaguchi T, Minx PJ, Cordum HS, Hillier LD, et al. 2003. The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. *Nature* 423:825–37
Slotkin RK, Martienssen R. 2007. Transposable elements and the epigenetic regulation of the genome. *Nat. Rev. Genet.* 8:272–85
Stajich JE, Dietrich FS, Roy SW. 2007. Comparative genomic analysis of fungal genomes reveals intron-rich ancestors. *Genome Biol.* 8:R223
Steinemann M, Steinemann S. 1997. The enigma of Y chromosome degeneration: TRAM, a novel retrotransposon is preferentially located on the Neo-Y chromosome of *Drosophila miranda*. *Genetics* 145:261–66
Stewart AD, Pischedda A, Rice WR. 2010. Resolving intralocus sexual conflict: genetic mechanisms and time frame. *J. Hered.* 101:S94–99
Straub T, Becker PB. 2007. Dosage compensation: the beginning and end of generalization. *Nat. Rev. Genet.* 8:47–57
Sweeny TL, Barr AR. 1978. Sex ratio distortion caused by meiotic drive in a mosquito, *Culex pipiens* L. *Genetics* 88:427–46
Tao Y, Araripe L, Kingan SB, Ke Y, Xiao H, Hartl DL. 2007. A sex-ratio meiotic drive system in *Drosophila simulans*. II: an X-linked distorter. *PLoS Biol.* 5:e293
van der Burgt A, Severing E, de Wit PJGM, Collemare J. 2012. Birth of new spliceosomal introns in fungi by multiplication of introner-like elements. *Curr. Biol.* 22:1260–65
Van Doorn G, Kirkpatrick M. 2007. Turnover of sex chromosomes induced by sexual conflict. *Nature* 449:909–12
Wade MJ, Brandvain Y. 2009. Reversing mother's curse: selection on male mitochondrial fitness effects. *Evolution* 6:1084–89
Werren JH. 2011. Selfish genetic elements, genetic conflict, and evolutionary innovation. *Proc. Natl. Acad. Sci. USA* 108:10863–70
Wigby S, Chapman T. 2005. Sex peptide causes mating costs in female *Drosophila melanogaster*. *Curr. Biol.* 15:316–21
Wolfner MF. 2009. Battle and ballet: molecular interactions between the sexes in *Drosophila*. *J. Hered.* 100:399–410
Worden AZ, Lee JH, Mock T, Rouzé P, Simmons MP, et al. 2009. Green evolution and dynamic adaptations revealed by genomes of the marine picoeukaryotes *Micromonas*. *Science* 324:268–72
Wright AE, Mank JE. 2012. Battle of the sexes: conflict over dosage-sensitive genes and the origin of X chromosome inactivation. *Proc. Natl. Acad. Sci. USA* 109:5144–45
Yang X, Schadt EE, Wang S, Wang H, Arnold AP, et al. 2006. Tissue-specific expression and regulation of sexually dimorphic genes in mice. *Genome Res.* 16:995–1004

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