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Evolutionary Dynamics and Consequences of Parthenogenesis in Vertebrates

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Abstract

Parthenogenesis is asexual reproduction without any required participation from males and, as such, is a null model for sexual reproduction. In a comparative context, we can expand our understanding of the evolution and ecology of sex by investigating the consequences of parthenogenesis. In this review, we examine the theoretical predictions of and empirical results on the evolution of asexual reproduction in vertebrates, focusing on recent studies addressing the origins and geographic spread of parthenogenetic lineages and the genomic consequences of an asexual life history. With advances in computational methods and genome technologies, researchers are poised to make rapid and significant progress in studying the origin and evolution of parthenogenesis in vertebrates, thus providing an important perspective on understanding biodiversity patterns of both asexual and sexual populations.

INTRODUCTION

Sex, reproduction that involves the fusion of recombinant gametes from distinct individuals, is foundational to multiple scientific and social disciplines, including human sexuality, demographics, sexual selection, reproduction biology, and development. Sexual reproduction is also ubiquitous across the tree of life. Thus, sex is a fundamental cellular mechanism, and understanding the origins and evolution of sexual reproduction continues to be a major goal in biology. Paradoxically, some of the best insights into understanding sex come from examining the evolution of asexual populations, in which individuals clone themselves from one generation to the next. Indeed, multiple theoretical and empirical studies have addressed the long-term evolutionary advantages of sex over asexual reproduction (reviewed in Otto 2009, Otto & Lenormand 2002), the most prominent of which are increased adaptive potential because of recombination and the purging of deleterious variants (Maynard-Smith 1978, Muller 1964). However, sex suffers a severe, twofold demographic disadvantage compared with asexual reproduction: Because asexual populations do not need to produce males, asexual populations can grow exponentially faster than sexual populations (Maynard-Smith 1978). Thus, for the long-term advantages to manifest, sexual populations must overcome the short-term demographic advantage of asexual populations (**Figure 1**). In this review, we discuss the evolutionary, genomic, molecular, and ecological mechanisms that influence the origin and evolution of asexual reproduction in vertebrates with the goal of understanding the dominance of sexual reproduction.

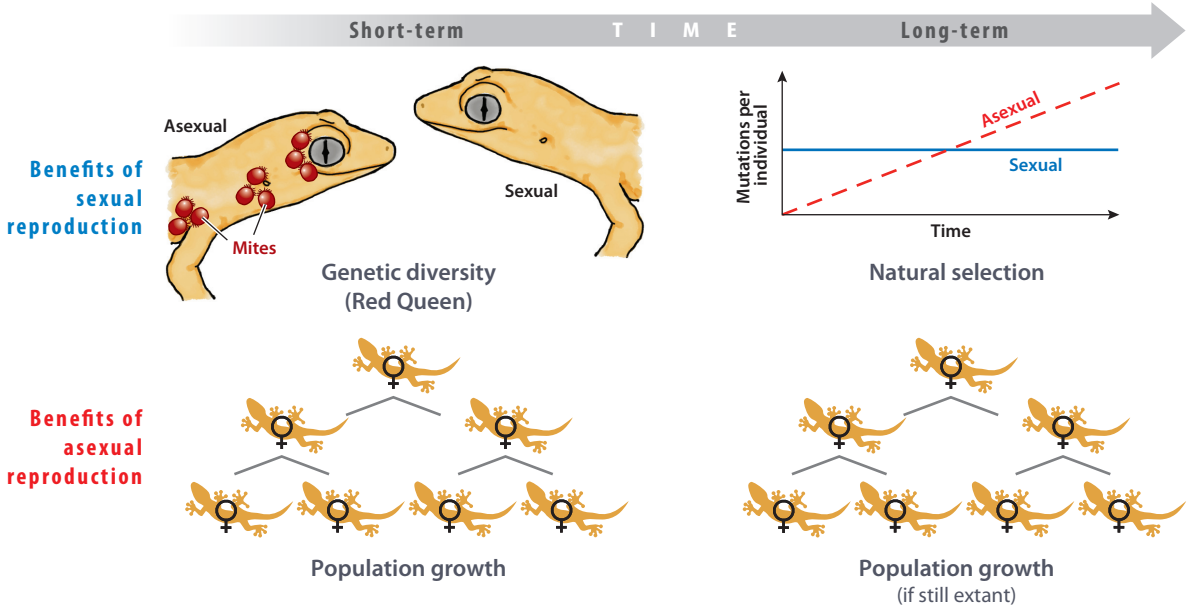

Figure 1

The benefits of sexual and asexual reproduction at both short-term and long-term scales theoretically apply to all organisms, though we demonstrate them here using lizards. Sex provides immediate benefits to a population because of standing genetic variation, which is an important contributor to adapting to rapidly changing environments, such as the involvement of frequency-dependent selection in host–parasite relationships. For example, greater genetic variation in sexual populations could provide resistance to parasites, such as mites, while asexual populations lack the diversity for that protection. Long-term benefits of sexual reproduction are centered around the efficacy of natural selection, allowing sexual populations to purge deleterious mutations but causing asexual populations to accumulate them. Asexual reproduction has an immediate demographic advantage, as populations can double with each generation. However, asexual reproduction has few, if any, advantages in the long term, and these populations will eventually go extinct.

Despite its rarity, asexual reproduction occurs across the tree of life by several distinct mechanisms. Parthenogenesis is a form of asexual reproduction by which females clone themselves without any contribution from males. This contrasts with other modes of vertebrate asexual reproduction exhibited by some fish, salamanders, and frogs, which require sperm to either (*a*) activate egg maturation (gynogenesis), (*b*) contribute to the zygote's genome (hybridogenesis, in which the paternal genomic complement is subsequently excluded during gametogenesis), or (*c*) occasionally contribute to the gene pool of asexual populations (kleptogenesis) (Avise 2008). Squamates (lizards and snakes) are the only vertebrates that reproduce via true parthenogenesis and thus maintain all-female populations. Facultative parthenogenesis occurs when a typically sexual organism reproduces without mating; such offspring may or may not be clones. Species of water fleas (*Daphnia*) are perhaps the best-known examples in which populations alternate between sexual and facultative parthenogenetic reproductive modes (reviewed in Decaestecker et al. 2009). However, several lizards and snakes also exhibit facultative parthenogenesis, with cases often observed in captivity when mateless females lay viable eggs (e.g., Miller et al. 2019, Watts et al. 2006) or even in wild populations (Booth et al. 2012). Lineages that exhibit obligate parthenogenesis, the subject of this review, reproduce asexually with no contributions from sex.

Although representing only 0.6% of lizard and snake diversity, obligate parthenogenetic lineages have arisen independently and multiple times in nine families across the squamate tree of life, providing natural and replicate experiments with which to study the evolution of asexuality in vertebrates (Kearney et al. 2009, Neaves & Baumann 2011, Sites et al. 2011). Some of the more intensely studied groups include the whiptail lizards (*Aspidoscelis*), rock lizards (*Darevskia*), and several groups of geckos (*Lepidodactylus* and *Heteronotia*), although other systems, such as Gymnophthalmidae: *Loxopholis* (Brunes et al. 2019) and Iguanidae: *Liolaemus parthenos* (Abdala et al. 2016), are beginning to provide important insights into the evolution of parthenogenesis.

As the only truly parthenogenetic vertebrates (and the only amniote group with obligate asexual lineages), squamates provide exceptional systems for investigating the consequences of asexuality on vertebrate populations and genomes. Parthenogenetic squamates invariably have hybrid origins: divergent, sexual progenitors hybridized to produce female offspring capable of clonal reproduction (**Figure 2**). Parthenogenetic lineages thus have a perpetually hybrid genome, composed of at least one complement from each parental species. Furthermore, backcrossing with one of the parentals, or even a third species, can result in triploid parthenogens (**Figure 2**). More rarely, tetraploidy has been observed in natural populations (Danielyan et al. 2008, Moritz 1984), although recent hybrid parthenogens were produced and maintained in the laboratory, confirming that stable tetraploid lineages can be established (Cole et al. 2017, Lutes et al. 2011). Thus, the genomes of parthenogenetic squamates are quite complex. In addition to being asexual, their hybrid and sometimes polyploid nature requires the cooperation of divergent genomic complements and perhaps some regulation to mediate gene dosage, as seen in gynogenetic *Ambystoma* salamanders (McElroy et al. 2017).

Despite the complexity of how vertebrate parthenogens originate, they remain valuable resources for investigating persistent questions about the evolution of sex because they are not immune to the disadvantages of asexual reproduction: Nearly all parthenogenetic vertebrates have a recent origin (but see Brunes et al. 2019), implying that extant lineages will rapidly go extinct (**Figure 2**). They are thus null models for sex and how sex influences evolution and ecology. Although we aim to summarize existing research (**Table 1**), we also provide a perspective not only on the persistent questions regarding the biology of parthenogens but also on how we can use parthenogens to address major evolutionary and ecological hypotheses, especially given new genomic approaches, ecological techniques, and laboratory-based methods (Griffing et al. 2019, Laskowski et al. 2019). Indeed, as genome-sequencing technologies progress, not just in volume of

Parthenogenesis: a mode of asexual evolution in which females clone themselves without any contribution from males

Gynogenesis: a mode of asexual evolution in which females clone themselves but require sperm to fertilize the egg; the sperm provides no genomic contribution but completes the egg's maturation

Hybridogenesis: a mode of asexual evolution in which females require fertilization for egg maturation, but the male genome is subsequently removed during gametogenesis in the offspring

Kleptogenesis: a mode of asexual evolution in which females require fertilization for egg maturation, and the male genome can contribute to the gene pool of the asexual population

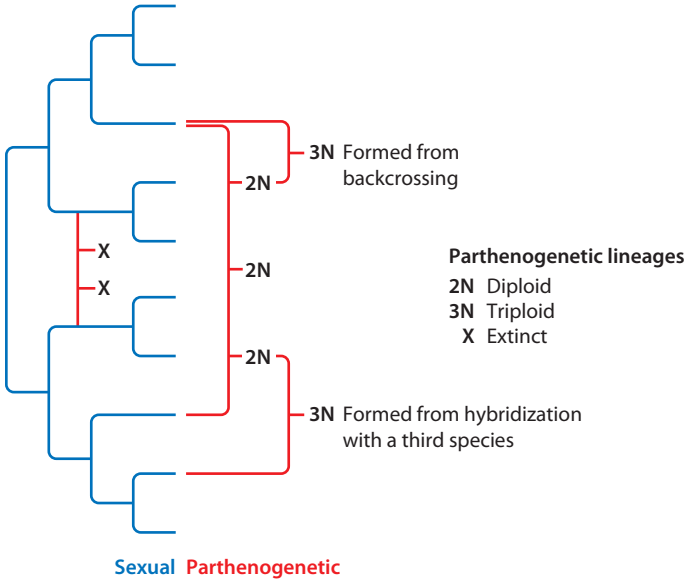

Figure 2

The formation of parthenogenetic lineages results from hybridization between divergent sexual progenitors. That the sexual progenitors are still extant provides strong evidence that parthenogenetic lineages have recent origins. Initially, diploid parthenogens (2N) are produced, but backcrossing or further hybridization with a third species can result in triploid lineages (3N). The formation of parthenogenetic lineages is likely not a contemporary phenomenon, though those that formed in deeper history have already gone extinct (X).

data but also in single-molecule, long-read capabilities (van Dijk et al. 2018), there is now an opportunity to address both persistent and emerging questions regarding the intimate connection between parthenogenesis in squamates and their complex genomes. Below, we highlight major questions that can leverage parthenogenetic systems:

1. How quickly do asexual genomes accumulate mutations? Mammals and birds provide insight into the long-term consequences of vertebrate asexual genome evolution with their heteromorphic sex chromosomes. However, parthenogenetic lizards and snakes can provide a view of mutation accumulation at short timescales on a whole-genome scale. Even though intergenomic recombination and gene conversion can act to shuffle or remove genetic variation, the genome still acts as a single linkage group and thus will not be immune to deleterious mutation accumulation. Furthermore, investigating the evolution of parthenogenetic genomes can identify the relative contributions of different kinds of mutations to early genomic deterioration [point mutations, insertions and deletions, transposable elements (TEs)].
2. Are epigenetic marks in parthenogens inherited stably through generations? In typical animal meiosis, epigenetic markers, such as CpG methyl groups, are removed and become reestablished during gametogenesis (Verhoeven & Preite 2014). In parthenogens, how and whether epigenetic marks are remodeled across generations are unknown, and remodeling might depend on the mechanism by which gametes are produced. Because epigenetic modifications of the genome can influence phenotype, understanding how epigenetic marks behave and evolve in an asexual genome can provide insight into phenotypic diversity in parthenogenetic lineages. Although epigenetic research on parthenogenetic vertebrates is

Gene conversion: the recombination-based mechanism by which the identity of one allele is replaced with another, resulting in a homozygous genotype

Table 1 Key studies of parthenogenetic squamates in evolution, ecology, and genomics

Study	Species	Main case study	Field of contribution
Cuellar 1979	*Aspidoscelis* spp.	Ecological comparison of sexual and parthenogenetic species	Ecology
Hanley et al. 1994	*Lepidodactylus* spp.	Niche differentiation and behavioral evolution between parthenogenetic and sexual species	Ecology
Kearney et al. 2003	*Heteronotia binoei* complex	Niche analyses between sexual and parthenogenetic geckos	Ecology
Petrosyan et al. 2019	*Darevskia armeniaca*	Ecological niche modeling analysis of parthenogenetic rock lizards	Ecology
Tarkhnishvili et al. 2010	*Darevskia* spp.	Comparisons of abundance and distribution in sexual and parthenogenetic lizards	Ecology
Hanley et al. 1995	*Lepidodactylus* spp.	Comparison of parasite infection frequency across naturally collected and experimentally exposed sexual and parthenogenetic geckos (Red Queen)	Evolution
Moritz et al. 1991	*Heteronotia binoei*	Parasite load comparison between sympatric parthenogenetic and sexual geckos (Red Queen)	Evolution
Lutes et al. 2011	*Aspidoscelis* spp.	Establishment of all female clonal tetraploid lizards	Evolution
Boussau et al. 2011	*Heteronotia binoei*	Influence on organelle genome size evolution in asexual geckos by effective population size	Molecular evolution
Fujita et al. 2007	*Heteronotia binoei*	Origins of large duplicated genes in asexual geckos	Molecular evolution
Hillis et al. 1991	*Heteronotia binoei*	Biased gene conversion toward one parental genotype in asexual geckos	Molecular evolution
Lutes et al. 2010	*Aspidoscelis* spp.	Maintenance of heterozygosity in asexual lizards by recombination between sister chromatids	Cell biology
Cuellar 1971	*Aspidoscelis uniparens*	Chromosome number doubling before entering meiosis in a triploid parthenogenetic lizard	Cell biology

in its infancy, they can provide insight into the replicability and stochasticity of epigenetic marks.

3. What cellular and genomic constraints must be overcome to allow a parthenogenetic lineage to become established? Meiosis and fertilization are fundamental developmental processes in eukaryotes, and their primary purpose is sex. However, asexual lineages must bypass (*a*) ploidy reduction, a hallmark consequence of meiosis, and (*b*) fertilization, or the restoration of diploidy by the fusion of male and female gametes. Furthermore, genomic imprinting is thought to be the mechanism that prevents parthenogenesis from occurring in mammals (Haig 2002). Parthenogenetic squamates are uniquely situated to teach us about the lability of these fundamental cellular and genetic mechanisms that allow parthenogenesis to evolve and, in a comparative context, teach us about the nature of the mammalian, and therefore human, genomes.
4. How do the genomic characteristics of parthenogenetic vertebrates influence their geographic distributions? Once formed, asexuals have a twofold demographic advantage and theoretically will rapidly outcompete their sexual progenitors and expand their range. However, vertebrate parthenogens also have limited genetic diversity and are hybrid, and some are polyploid. Research on understanding niche evolution between asexuals and sexuals has been useful for predicting the origin and maintenance of parthenogenetic species in nature,

Genomic imprinting: the parent-of-origin expression of alleles as a result of epigenetic regulation

and future studies can additionally integrate genomics and modeling to examine how the dynamic genome of parthenogens affects their distributions.

Hill–Robertson interference: the reduction in selection efficiency as a result of reduced effective population size caused by genetic linkage

Muller's ratchet: the gradual accumulation of deleterious mutations that leads to decreased fitness of an asexual population over time

Red Queen hypothesis: the hypothesis that two species are in an antagonistic arms race in a constantly changing environment

BENEFITS OF SEXUAL AND ASEXUAL REPRODUCTION

An enduring puzzle in evolutionary biology is why sex has been so successful despite its many costs. Darwin (1862, p. 94) wrote, "We do not even in the least know the final cause of sexuality; why new beings should be produced by the union of the two sexual elements, instead of by a process of parthenogenesis." This long-standing question has led to the proposal of more than 20 hypotheses that explain the short- and long-term advantages of sexual over asexual reproduction (Meirmans & Strand 2010). Maynard-Smith (1978) summarized the primary conundrum: Because an asexual population can grow more quickly than a sexual population, it will outcompete the sexual population before the long-term benefits of sex manifest (twofold cost of sex) (**Figure 1**). Sex is also physically costly because it requires finding mates (Daly 1978). Furthermore, sex can disrupt coadapted gene complexes (Agrawal 2006), presumably resulting in sexual offspring that are less fit than their parthenogenetic relatives. Given these disadvantages, what are the short-term benefits of sexual reproduction that can outweigh the demographic advantages of an asexual population?

Most hypotheses explaining the dominance of sexual reproduction fall into two main categories, both of which are based on natural selection. First, sex facilitates the removal of deleterious mutations from populations (mutation-recombination model). Linkage reduces the effective population size of linked genes, which in turn weakens the strength of selection compared with genetic drift (Hill-Robertson interference; Hill & Robertson 1966). In parthenogenetic populations, whole genomes are linked together; thus, genetic drift strongly influences the trajectory of new mutations, allowing deleterious variants to reach fixation due to the depressed efficacy of purifying selection. Mutations irreversibly accumulate through generations, reducing the fitness of individuals and eventually leading to the extinction of a population (this irreversible accumulation of mutations in an asexual population is known as Muller's ratchet; Muller 1964). Conversely, sex reduces linkage disequilibrium, which increases the effective population size of linked genes, and thus allows selection to more effectively remove deleterious mutations, avoiding Muller's ratchet. Purging deleterious mutations is likely a long-term advantage of sex, but it is unlikely to outweigh the immediate twofold demographic advantage of asexual reproduction. For this to be true, mutations must arise so quickly that the fitness of asexual populations—and thus reproductive output—drops significantly, preventing them from outcompeting their sexual progenitors (Charlesworth 1990, Kondrashov 1988). Genome-sequencing technologies now provide the capabilities to quantify mutation rates in both asexual and sexual populations at the whole-genome scale, which allows researchers to (*a*) address whether rates are disparate between sexuals and asexuals and (*b*) model the fitness decline of asexual populations as a result of mutation accumulation.

Second, sex accelerates adaptive evolution by increasing the probability of fixation of favorable alleles by bringing them together via segregation and recombination. This allows new genotypes to form quickly, which is beneficial when environmental conditions change rapidly. As predicted by the Red Queen hypothesis (Bell 1982), the constant generation of new combinations of alleles should enable sexual populations to adapt to rapidly changing environments, thus avoiding extinction (Becks & Agrawal 2012). Asexually reproducing populations are unable to generate novel genotypic combinations as quickly and thus have difficulty adapting to new environments. Unlike Muller's ratchet, which is a long-term consequence of asexual genome evolution, the Red Queen acts at shorter ecological timescales. That is, adaptive potential is a short-term advantage of sex that could act against the short-term demographic advantage of asexual reproduction. Support for the

Red Queen hypothesis in parthenogenetic vertebrates comes from studies of parasite (mite) load on the Bynoe's gecko (*Heteronotia binoei*) from Australia (Moritz et al. 1991). Parasites are hypothesized to have evolved resistance to the host's most common defense genotypes. With their static genomes, parthenogenetic individuals all have the same genotype and are thus expected to carry high parasite loads. Sexual populations will have diverse genotypes that will fluctuate in frequency on the basis of the resistance they provide against the parasites (frequency-dependent selection). Thus, sexual individuals are expected to have a lower parasite load than parthenogens, a prediction supported by sympatric populations of sexual and parthenogenetic Bynoe's geckos (Moritz et al. 1991). However, the opposite pattern was found in parthenogenetic mourning geckos (*Lepidodactylus lugubris*) and rock lizards (*Darevskia*), in which asexual populations had parasite loads lower than or equivalent to parasite loads on closely related sexual species (Arakelyan et al. 2019, Hanley et al. 1995). For the geckos, this unexpected pattern of lower load in the asexual species might be driven, in part, by lower genetic diversity in sexual island populations.

The major histocompatibility complex (MHC) may play a role in evading parasites (Jeffery & Bangham 2000, Radwan et al. 2020), thus providing a functional genetic link in the Red Queen hypothesis for host–parasite interactions. As expected, empirical data have shown that parthenogenetic geckos (*L. lugubris* and *Hemidactylus garnotii*) have lower levels of polymorphism, but higher heterozygosity, at MHC class I genes compared with their sexual relatives (Radtkey et al. 1996). This high heterozygosity in the parthenogens might provide a resistance to parasites that is superior to that for sexuals, thus explaining the greater mite loads on sexual individuals than on parthenogenetic individuals. The link between the MHC and the Red Queen hypothesis for host–parasite interactions has yet to be established for squamates, let alone for parthenogens. Future research should integrate estimates of genetic diversity, including a focus on genes involved in parasite resistance, with field studies of parasite load.

The near absence of ancient parthenogenetic vertebrate lineages indicates that the unique problems they face, such as accumulating parasite and mutation loads, will rapidly drive asexual lineages to extinction. Identifying the long- and short-term advantages of sex sufficient to overcome the demographic advantage of asexual reproduction continues to be an important goal in understanding the origin and evolution of vertebrate parthenogens. A combination of factors, including Red Queen dynamics, likely affects the short-term success of asexual lineages (Neiman et al. 2017).

PERSPECTIVE FROM MOLECULAR AND CELLULAR BIOLOGY

Any transition to asexuality in eukaryotes must overcome two major features of sexual reproduction: ploidy reduction via meiosis and ploidy restoration via fertilization. Meiosis is a fundamental developmental process in eukaryotes that creates genetically distinct haploid gametes via two meiotic stages. During meiosis I, recombination creates new variation in prophase I, and an independent assortment of chromosomes further generates new variation in metaphase I and anaphase I. In animals, oocytes arrest in metaphase II and finish maturing only when stimulated by sperm and a subsequent influx of cytoplasmic calcium (Ca^{2+}) (Rauh et al. 2005). Fertilization thus has two primary purposes: to induce egg maturation and to restore diploidy by fusing two gametes. Parthenogens do not have sex but still produce unreduced eggs; they have overcome both of these constraints of sexual reproduction. Furthermore, the cellular mechanism of obligate parthenogenesis must also maintain the high heterozygosity seen in most parthenogenetic vertebrates across generations if reproduction is clonal. Thus, parthenogenetic lizards offer an exceptional opportunity to investigate the cellular mechanisms that allow the tinkering of fundamental developmental processes in order to allow asexual reproduction.

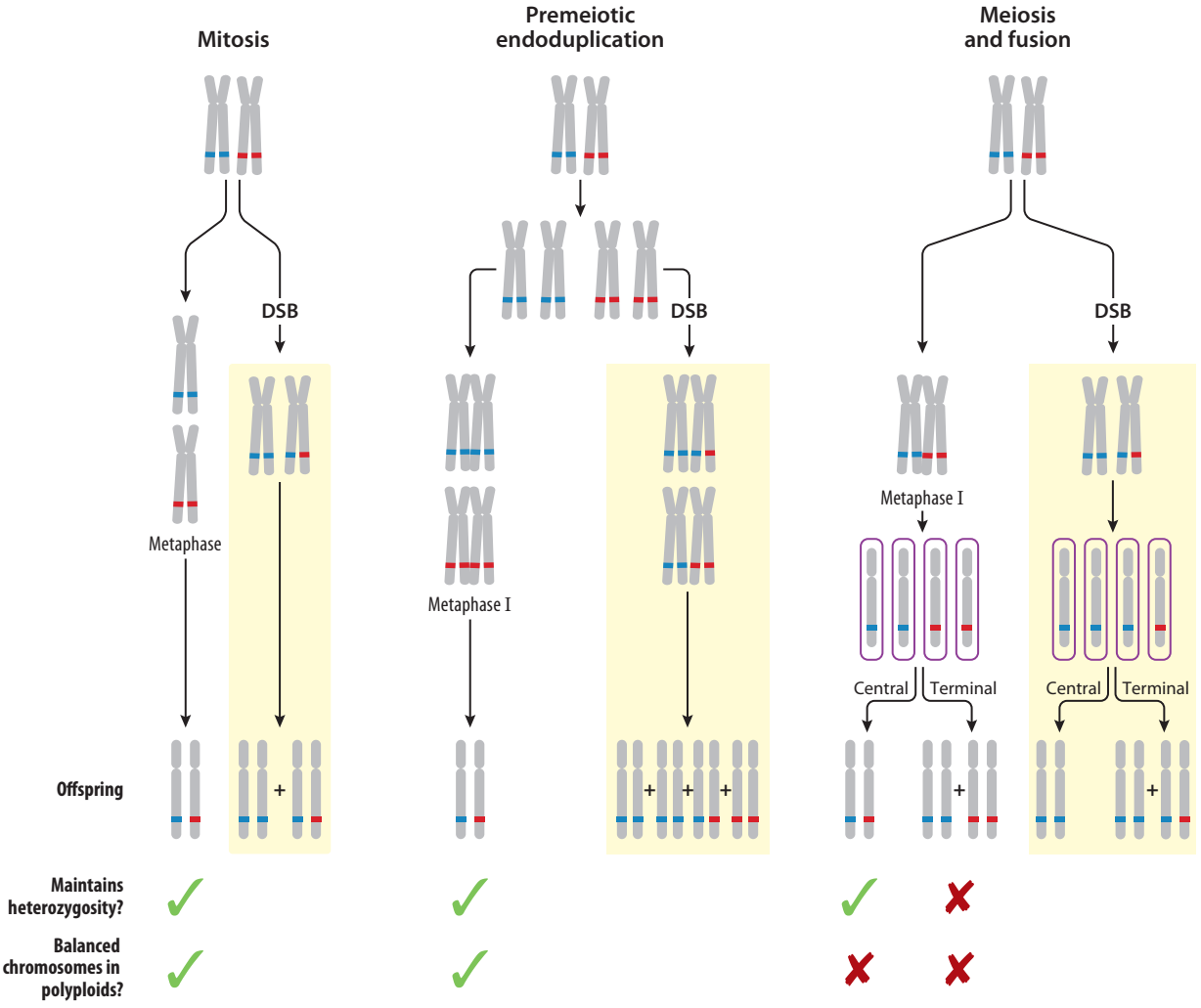

Figure 3

The three major mechanisms (mitosis, premeiotic endoduplication, and meiosis with central or terminal fusion) for producing zygotes in asexual species. We track gamete and zygote formation starting with a heterozygous parent. Red and blue bands indicate alternate alleles at the same locus. The purple boxes represent cells, in this case gametes. We note if these mechanisms can maintain the high heterozygosity seen in many parthenogenetic vertebrates and if they can create zygotes with a balanced chromosome number in polyploids. Further shown are how these mechanisms interact with crossing over and gene conversion following double-strand breaks (DSBs); outcomes resulting from DSBs are backgrounded in yellow. For simplicity, only gene conversion following repair from a homologous or homeologous chromosome is shown.

The cellular mechanism of parthenogenesis has been studied in most detail in whiptail lizards (*Aspidoscelis*), and these studies found that asexual species produce unreduced, clonal, and genetically identical eggs via meiosis (as opposed to other cellular mechanisms) (Cuellar 1971, Lutes et al. 2010) (**Figure 3**). Cuellar (1971) noticed that oocytes at the metaphase II arrest had twice as much DNA as expected, implying the presence of a mechanism that doubles the amount of DNA entering meiosis. Uzzell (1970) suggested that these lizards employed premeiotic endoduplication, or a duplication of the DNA prior to entering meiosis. Using microscopy and DNA

quantification methods, Lutes et al. (2010) provided convincing evidence for the presence of both premeiotic endoduplication and meiosis in the parthenogenetic whiptail lizard *Aspidoscelis tesselata*. Thus, the hypothesized mechanism for parthenogenesis involves (*a*) a second doubling of DNA prior to entering meiosis, (*b*) pairing of identical chromosomes during prophase I, and (*c*) production of unreduced eggs during meiosis II.

In other invertebrates or facultative vertebrate systems, two other mechanisms are used to generate diploid zygotes, and these mechanisms might also act in uncharacterized obligate parthenogenetic systems (**Figure 3**). First, multiple invertebrates use mitosis to produce diploid zygotes from germline cells. Second, some facultative vertebrate systems generate diploid zygotes via normal meiosis (without premeiotic endoduplication) followed by fusion of oocytes. In terminal fusion, oocytes with identical chromosomes combine, producing diploid, highly homozygous eggs. Central fusion combines oocytes with homologous or homeologous chromosomes, maintaining heterozygosity. Alternatively, diploid cells could form if karyokinesis and cytokinesis fail during the final stage of meiosis. However, fusion of any kind is unlikely to be the mechanism in triploid species because it would result in the production of aneuploid eggs.

At least three primary questions about the cellular mechanisms of obligate parthenogenesis remain. First, what are the mechanisms by which gametes are produced across the independent origins of squamate parthenogenesis? If the same mechanism is responsible for parthenogenesis across divergent lineages, then this implies that strong developmental constraints limit the evolution of asexuality. Second, if there are two rounds of DNA replication prior to meiosis, what is the mechanism of this premeiotic endoduplication? The two primary hypotheses for this are two rounds of DNA synthesis, or as hypothesized by Uzzell (1970), a failure of the final mitotic division of premature oocytes could result in twice the expected genomic content prior to entering meiosis. Third, in the absence of fertilization from sperm, what triggers eggs to mature?

In addition to the cellular and developmental constraints, there are genomic processes that could constrain the evolution of asexual reproduction. For example, genomic imprinting, an epigenetic mechanism that governs the parent-of-origin expression of alleles, is hypothesized to prevent parthenogenesis in mammals (Haig 2002). Genomic imprinting is thought to have evolved because mothers and fathers have conflicting fitness benefits in how they should partition resources to developing offspring (kinship theory; Haig 2002). At a small subset of genes, mothers and fathers imprint alleles at loci differently, leading to only the maternal or paternal copy of the allele being expressed in the embryo. Imprinting necessitates both parental genomes to properly modulate gene expression during development. In parthenogenetic animals, offspring inherit only maternal alleles and maternal expression patterns. Loci that are typically paternally imprinted would be transcriptionally silenced and unable to contribute to the proper development of the embryo (Kono et al. 2004). Thus, genomic imprinting imparts a powerful constraint that forces biparental (and therefore sexual) reproduction.

The evolution of genomic imprinting in reptiles is unknown (Renfree et al. 2013). On the basis of kinship theory, genomic imprinting is most likely to have evolved in viviparous squamates because maternal input into offspring care is greater than paternal input. If genomic imprinting has evolved in squamates, then squamates, with their independent origins of parthenogenesis and viviparity, provide an excellent system to test whether epigenetics plays a role in constraining the evolution of asexual reproduction. We predict that the ancestral state in clades with parthenogenetic lineages lacked genomic imprinting or that imprinting was lost in the transition to asexuality. We would further expect parthenogenesis to have evolved mainly in oviparous (egg laying) lineages. These open questions emphasize how squamates and parthenogens can uniquely provide novel insights into important genomic mechanisms.

Premeiotic endoduplication: a second doubling of the genome prior to entering meiosis, which allows the formation of unreduced gametes during gametogenesis

Epigenetics: alterations to the physical state of DNA, but not its sequence, that result in modified gene regulation

PERSPECTIVE FROM EVOLUTIONARY GENETICS

Geographic parthenogenesis: the distribution pattern of parthenogens, which describes their tendency to inhabit and populate marginal areas, islands, higher latitudes and altitudes, and disturbed habitats, compared with that of their sexual relatives

Three distinct but interacting features of vertebrate parthenogens drive their evolutionary dynamics. First, almost all vertebrate parthenogens arise from hybridization between species with distinct genomes (but see *Lepidophyma*; Sinclair et al. 2010). As seen with hybridization more generally, admixture can result in reduced fitness due to negative epistasis across loci or heterozygote disadvantage within loci (Coyne & Orr 2004). By contrast, hybridization can also lead to heterosis, which could provide the parthenogens with an immediate selective advantage over their sexual progenitors. Additionally, in squamates, approximately 40% of these hybridization events result in polyploidization (Kearney et al. 2009); an additional set(s) of chromosomes can both provide a new substrate for evolution and require the evolution of new forms of dosage compensation. Second, the lack of recombination in parthenogens can further subject them to decreased fitness over evolutionary time (Muller 1964) and delay the rate of adaptive evolution (Hill & Robertson 1966, Maynard-Smith 1978). Finally, many vertebrate parthenogens have a distinctive demographic history, in which multiple clones form and then quickly spread at the habitat margins of their parental species (e.g., geographic parthenogenesis). This combination of hybridization, polyploidization, demographic history, and asexuality interacts to influence how parthenogenetic genomes evolve. To date, most evolutionary genetic research on vertebrate parthenogens [e.g., *Aspidoscelis* (Barley et al. 2019), *Darevskia* (Freitas et al. 2016), *Leiolepis* (Grismer et al. 2014), *Leposoma* (Pellegrino et al. 2011), and *Menetia* (Adams et al. 2003b)] has explored their evolutionary origins and demographic history. This work has also clarified when and where parthenogenesis has evolved across squamates (Booth & Schuett 2016, Kearney et al. 2009, Sites et al. 2011). Understanding the phylogenetic distribution of parthenogenesis might further help clarify the developmental and evolutionary constraints on parthenogenesis. In this section of the review, we explore how we can build on these foundational studies to better understand the evolutionary constraints faced by parthenogens and their possible evolutionary trajectories.

Constraints of Hybrid and Polyploid Genomes

Hybrid genomes lead to extensive new interactions among loci, both across alleles within a locus and across alleles between loci. In sexual hybrid species, the genome stabilizes as negative epistatic interactions are lost through the differential sorting of parental alleles (e.g., in hybrid sparrows; Runemark et al. 2018). However, in hybrid parthenogens, there is no opportunity for extensive recombination and restructuring to minimize the hybrid load of the genome. Thus, the hybrid parthenogenetic species we see today likely reflect a small fraction of those that have formed historically; many hybrid parthenogens that were formed were likely quickly lost due to overwhelming hybrid load (Blanckaert & Bank 2018). This hybrid load results from both Dobzhansky–Muller incompatibilities and cytonuclear incompatibilities, which together can decrease overall individual fitness. Some evidence for hybrid load has been seen in *Heteronotia*, *Darevskia*, and *Aspidoscelis* asexual lizards (Abramjan et al. 2019, Cullum 1997, Kearney & Shine 2004), although isolating the effects of a hybrid genome from those of an asexual genome can be challenging. However, hybrid genomes can also lead to heterosis, or increased hybrid vigor, as is commonly seen in plants (Lippman & Zamir 2007), or, for a given locus, heterozygote advantage. Under what conditions mixing two genomes is more likely to result in negative epistasis versus heterosis is unknown, though it likely varies as a function of genetic divergence between the two genomes (Wei & Zhang 2018). And, as predicted by the balance hypothesis, the two parental genomes must be similar enough that hybrids are viable and fertile but different enough that meiosis is disrupted in hybrids (Moritz et al. 1989, Murphy et al. 2000).

Polyploid parthenogens have an extra set of chromosomes as a result of backcrossing with one of the parentals or perhaps an entirely distinct third sexual species. Such backcrossing poses several distinct challenges. First, polyploid species have increased mutational load, simply because they have more chromosomes carrying more mutations. However, if these mutations are recessive, the additional chromosomal copies can help hide the phenotypic effects of these mutations. Second, more gene copies typically result in more gene expression. Many polyploid vertebrates have evolved genome-wide dosage compensation such that expression levels remain more similar to those of a diploid organism, as seen in bisexual polyploid fish (Ren et al. 2017) and unisexual polyploid fish (Li et al. 2014). Ploidy can be most challenging for sex chromosomes, for which most vertebrates show some form of dosage compensation in the diploid state (Mank 2009). Whether males or females are the heterogametic sex, polyploidization can disrupt dosage compensation, which is perhaps why polyploidization is so much rarer in animals than in plants (Orr 1990). As a corollary, we might predict that most parthenogenetic polyploids should have sex chromosomes that are homomorphic or weakly heteromorphic. This prediction has yet to be tested, though many parthenogenetic vertebrates appear to lack differentiated sex chromosomes [e.g., *Heteronotia* geckos (Moritz 1984) and *Loxopholis* lizards (Pellegrino et al. 1999), but see *Lepidodactylus lugubris* geckos (Volobouev & Pasteur 1988)].

Sources of Genetic Variation

The genomes of parthenogens are often considered frozen because they capture their parental genomes at a particular point in time and then clonally reproduce. However, parthenogenetic genomes are dynamic due to mutation, recombination, gene conversion, and gene regulation. Note that some obligate parthenogens can still reproduce sexually with a diploid ancestor (Brunes et al. 2019, Danielyan et al. 2008), which can result in introgression of new alleles. However, such introgression events in obligate parthenogens are expected to be fairly rare (Moritz 1984); thus, we do not further discuss this potential source of variation.

Mutation. Not only are substitution rates expected to be higher in asexual lineages than in sexual lineages (see the section titled Mutation Accumulation), the raw mutation rate might also be higher in asexual lineages. From a mechanistic perspective, the genomic stress of hybridization and polyploidization can decrease the efficacy of DNA repair, increasing de novo mutation rates (Bashir et al. 2014). Further, mutation rate itself can evolve to be higher, because modifier mutations that increase the mutation rate can more easily spread in asexual populations due to the lack of recombination (Hurst 2009). However, other evidence suggests the raw mutation rate might be lower in asexual species than in sexual species. First, double-strand breaks (DSBs) and their associated repair can result in new mutations (Gao et al. 2019), so if DSBs form less frequently in asexual species as expected, then this might lead to a decreased mutation rate. Second, in some vertebrate species, including humans (Kong et al. 2012), the male germline has a significantly higher de novo mutation rate than that of the female germline (Gao et al. 2019). Without males, unisexual species might thus have decreased mutation rates. Whether or not asexual species have higher mutation rates than sexual species, alleles at a given locus, which often initially show high sequence divergence due to the hybrid origins of a parthenogen, should continue to diverge only as they accumulate new mutations, leading to increasing heterozygosity over time (e.g., the Meselson effect; Birky 1996, Mark Welch & Meselson 2000).

Recombination and gene conversion. Regardless of the mechanism of parthenogenesis (mitotic or meiotic), parthenogens can have some form of recombination via DSBs (**Figure 3**). In

both sexual and asexual lineages, DSBs can result due to either DNA damage or cellular machinery that generates breaks; these DSBs are then resolved to result in either crossovers or noncrossovers, both of which can result in heteroduplex DNA. Gene conversion results from repairs to base mismatches in heteroduplex DNA (Chen et al. 2007). For parthenogens that make eggs via mitosis, DSBs that are repaired with the homologous chromosome versus the sister chromatid can result in mitotic recombination. For parthenogens that have premeiotic doubling of chromosomes followed by meiosis (the expectation in vertebrates), crossing over can occur if chromosomes synapse with homologous or homeologous chromosomes instead of their identical, newly copied chromosome. How probable such a synapsis is to occur likely depends on both absolute sequence divergence and structural variation between homologous and homeologous chromosomes. If the homologs or homeologs are too divergent, then synaptic pairing might be impaired, preventing repair and meiosis, as seen in whiptail lizards (Newton et al. 2016) and *Darevskia* lizards (Spangenberg et al. 2017). For parthenogens using fusion of haploid gametes following meiosis, DSBs can occur as expected. In addition, across reproductive mechanisms, gene conversion is possible following hairpin formation in palindromic sequences or following ectopic recombination across paralogous regions. Moving forward, we should characterize the relative frequency of DSBs in parthenogenetic species versus sexual species and determine what factors affect the likelihood of repair from sister chromatids versus between homologous or homeologous chromosomes. These data will help us understand the importance of recombination and gene conversion in the genome evolution of asexual species.

Although we would expect overall rates of crossing over and gene conversion to be lower in parthenogenetic species than in sexual species, they might still occur at levels high enough to appreciably affect genome dynamics, as has been seen in the bdelloid rotifer (Flot et al. 2013) and the Amazon molly (Warren et al. 2018). In hybrid parthenogens, heterozygosity is initially high across the genome, but over time loss of heterozygosity (LOH) can occur as gene conversion converts heterozygous sites to homozygous sites. This can lead to either the immediate loss of a deleterious allele or its more gradual loss because it is exposed to selection in a homozygous state. Either way, LOH should eventually decrease the overall mutational load of a population. Further, gene conversion can be biased toward one parental allele versus another, such as in parthenogenetic *Heteronotia* lizards, in which ribosomal DNA is converted preferentially toward one parental type (Hillis et al. 1991). The relative influences of the variation-generating mechanism of recombination and the variation-depleting mechanism of gene conversion, combined with the influx of new variation via mutation, have yet to be characterized in a vertebrate parthenogen. Moving forward, we should determine how these competing mechanisms either quicken or slow genomic deterioration in parthenogenetic species.

Gene regulation. Gene regulation can serve as an important source of phenotypic variation in parthenogens, particularly those of hybrid and polyploid origin. At the point of parthenogen formation, we might predict a sudden and pervasive change in gene expression as two divergent genomes with different epigenetic marks and different alleles for regulatory factors combine within a single individual (e.g., transcriptomic shock; Hegarty et al. 2006). Our null expectation is that parental alleles in parthenogenetic hybrids should show balanced gene expression. However, for some genes, we might see allele-specific expression (ASE), or changes to gene regulation such that only one parental allele is largely transcribed and translated. Studies of polyploid vertebrates have found that this pattern can be dynamic across both genes and tissues (Pala et al. 2008), though the pervasiveness of expression biases across the genome and across tissues remains unknown. Across different vertebrate hybrid species, anywhere from 4% to ~30% of genes show biased expression toward one of the parents (McElroy et al. 2017, Ren et al. 2016, Warren et al.

2018). Even if the fraction of differentially expressed genes is small, ASE can increase the range of phenotypic variation in a hybrid genome and can potentially mitigate hybrid load by silencing alleles in negative epistasis.

Epigenetic marks are one important mechanism by which genes are regulated, and these marks can serve as an important source of variation in asexual species. In sexual vertebrate species, most epigenetic marks are reset at meiosis and then again at fertilization (Verhoeven & Preite 2014). How epigenetic marks change across generations in parthenogenetic species is unknown, though it likely depends on whether eggs are reproduced via mitosis or via a modified meiotic pathway (**Figure 3**). In either case, the initial founding of a parthenogenetic lineage likely serves as an epigenetic reset, because both hybridization and polyploidization can trigger a massive shift in epigenetic marks genome-wide (Rapp & Wendel 2005). Once reset, these epigenetic marks can change as the environment changes. Profiling of epigenetic marks has found that parthenogenetic populations in different environments have distinct marks, which might enable their survival in those habitats (Castonguay & Angers 2012, Verhoeven & Preite 2014). Future research should investigate how gene regulation and epigenetics contribute to phenotypic variation in parthenogenetic vertebrates and whether they allow parthenogenetic species to quickly acclimate to changing environmental conditions despite otherwise slow rates of adaptation.

Mutation Accumulation

One argument for the ubiquity of sex is that sexual populations are better able to purge deleterious mutations and thus have a lower genetic load (see the section titled Benefits of Sexual and Asexual Reproduction). Muller's ratchet might explain the rarity of asexual species and why obligate asexuality is an evolutionary dead end. Numerous theoretical and experimental studies support these classical predictions (Desai et al. 2007), but few empirical studies have investigated mutation accumulation between asexual and sexual taxa. Most studies have sampled a small portion of the genome, and only a few have studied patterns across the genome. Two distinct approaches have been used to test whether asexual lineages are accumulating mutations at a faster rate than sexual lineages are. First, for coding regions, we can estimate mutation accumulation by calculating the ratio of nonsynonymous to synonymous substitutions (dN/dS). Because nonsynonymous mutations are changes to the amino acid sequence, they are often assumed to be deleterious. Thus, a higher dN/dS in asexual versus sexual lineages is interpreted as evidence for increased mutation accumulation. Second, we can quantify the level of heterozygosity between asexual and sexual species. In asexual species, allele copies should become more heterozygous over time as they accumulate independent mutations. Further, with the right sampling, we can test our expectations both for mutations segregating in asexual versus sexual populations and for mutations fixed in one population or another (e.g., Bast et al. 2018, Hollister et al. 2015) in order to disentangle the relative roles of selection, mutation, and recombination on variation through time.

Across both approaches, results have been mixed. Evidence of mutation accumulation has been found in asexual snails, stick insects, and plants (Bast et al. 2018, Henry et al. 2012, Hollister et al. 2015, Lovell et al. 2017, Neiman et al. 2010). However, two asexual aphid lineages had no evidence of increased mutation accumulation in the mitochondrial genes, and only one asexual lineage had increased mutation accumulation in a nuclear gene (Normark & Moran 2000). One whole-genome-wide study of asexual mites found that selection was more efficient in asexual lineages than in sexual lineages, contrary to expectations (Brandt et al. 2017). Studies of mutation accumulation in parthenogenetic vertebrates are rare (Boussau et al. 2011). Our best evidence for the role of clonal inheritance in mutation accumulation in vertebrates comes from the nonrecombining regions of the mammalian Y and avian W sex chromosomes. These chromosomes

have evolved multiple times (Vicoso 2019), and across these independent evolutions, they have accumulated mutations and deteriorated to host just a few protein-coding genes.

The conflicting results for mutation accumulation likely arise from three issues. First, many of these studies have sampled only a few loci; thus, these studies might be simply underpowered. Second, some of these studies likely sampled younger asexual lineages, in which the effects of mutation accumulation are more subtle and harder to capture than those in older lineages. Third, many asexual lineages still experience crossing over and gene conversion (see the section titled Sources of Genetic Variation), albeit likely more rarely than sexual lineages. Gene conversion can reduce heterozygosity, and this, along with rare crossing over, might counteract the effects of asexuality (Otto & Barton 1997). Given these conflicting results, it remains uncertain whether mutation accumulation is a direct consequence of asexuality. Future studies using whole-genome data across a broader diversity of asexual taxa will be key to address this long-standing question of mutation accumulation in parthenogenetic vertebrates.

Genome Evolution

Parthenogens may also evolve broadscale genomic changes relative to their sexual relatives due to the changed behavior of transposable elements and to shifts in sources of selection on their genomes.

Transposable elements. TEs are self-replicating genomic units that are generally considered parasites of the genome because they spread at a cost to host fitness. Depending on their insertion patterns, TEs can change gene expression patterns, trigger structural rearrangements, and disrupt coding sequence (Kidwell & Lisch 2000). As predicted with other deleterious mutations, parthenogenetic genomes should be less effective than sexual genomes at purging TEs (e.g., Hill–Robertson interference; Hill & Robertson 1966), ultimately increasing TE density in the genome. Further, both hybridization and polyploidization can trigger genomic shock and the spread of TEs (McClintock 1984, Wendel 2000). However, asexuality can also lead to the evolution of less parasitic TEs. In sexual populations, highly active TEs have increased fitness because they can quickly spread through populations and genomes. In asexual populations, the lack of sex permanently couples the fitness of the host genome and the TE, which can eventually lead to selection for benign TEs and decreases in overall TE load (Bast et al. 2016). Indeed, if neither more benign TEs nor better control mechanisms from the host genome (e.g., increased excision rates) evolve, TE proliferation can lead to lineage extinction, leaving behind only those asexual lineages with lower TE loads (Nuzhdin & Petrov 2003). Given that strong verbal arguments both support and oppose increased TE spread in parthenogenetic genomes, and that these arguments act at different timescales, it is unsurprising that evidence for increased TE load has been equivocal across diverse asexual species, such as stick insects, *Daphnia* water fleas, rotifers, and yeasts (Bast et al. 2016, 2019; Schaack et al. 2010). For vertebrates, species-wide tests have been restricted to the gynogenetic Amazon molly, in which no significant difference in TE density between asexual and sexual lineages was found (Warren et al. 2018). Characterizing TE density across parthenogenetic species with different ages, different ploidy levels, and varying genetic divergences between parental species will help us understand how these factors influence TE spread.

Relaxed selection. Parthenogenesis can lead to changes in the selection dynamics in the genome both generally and across specific loci groups. First, because parthenogenesis in vertebrates often leads to ploidy changes, the additional set of chromosomes provides a new substrate for evolution. Gene or genome duplication can lead to neofunctionalization, subfunctionalization,

pseudogenization, and gene loss (Lynch & Walsh 2007). Although we know of no cases in hybrid parthenogens, changes in gene function across copies have been seen in other polyploid species, such as in the repeated origins of tetraploid cotton (Adams et al. 2003a).

Second, sexual selection and sexual conflict are hypothesized to be major drivers of the differences in gene expression seen between sexes across diverse species (Parsch & Ellegren 2013). Accordingly, species that experience weaker sexual selection or sexual conflict also show reduced sexual dimorphism in gene expression (Harrison et al. 2015). For parthenogenetic lineages, which experience no sexual selection, we might expect a similar pattern. This hypothesis has been tested only in stick insects. Surprisingly, genes that had female-biased expression in sexual species showed decreased expression in asexual females, whereas male-biased genes showed increased expression (Parker et al. 2019). How this might affect parthenogenetic vertebrates—and whether these changes are likely to be due solely to epigenetic factors rather than genetic factors—remains an open question.

Finally, loss of a trait can also lead to decay in the genes that encode the trait. Depending on how parthenogens produce zygotes (**Figure 3**), we might predict to see decay in genes specific to male-related processes (e.g., spermatogenesis) or in meiosis-related and sexual trait genes more generally (van der Kooi & Schwander 2014). Thus far, several asexual invertebrate genomes (e.g., the marbled crayfish and the *Caenorhabditis briggsae* nematode) show pseudogenization and loss of such genes in support of this hypothesis (Gutekunst et al. 2018, Yin et al. 2018). In the Amazon molly, however, no such evidence was found, which might reflect the recency of the transition to asexuality in this species, the active use of these genes in the gynogenetic reproductive mode, or both (Warren et al. 2018). Degeneration of such genes would make transitions back to sexuality difficult (e.g., Dollo's law of irreversibility), and this biased transition rate could, in part, contribute to the twiggy distribution of asexuality on the tree of life.

PERSPECTIVE FROM EVOLUTIONARY ECOLOGY

Compared with their sexual relatives, parthenogenetic species frequently have larger distributions and often occur in marginal areas, at higher latitudes and altitudes, in more open areas, on islands, and in disturbed habitats (but see Cosentino et al. 2019) (**Table 2**). Further, closely related asexual and sexual species often have present-day nonoverlapping distributions. This overall pattern is known as geographic parthenogenesis (Kearney 2005), and in this section, we review the primary genomic, historical, and ecological explanations for geographic parthenogenesis in vertebrates.

Genomic Explanations for Geographic Parthenogenesis

Given that most vertebrate parthenogens arose from hybridization events, heterosis itself might explain why they inhabit peripheral areas or regions with characteristics intermediate to those occupied by parental species (Kearney 2005). Further, many vertebrate parthenogenetic species are also polyploids. The increase of ploidy through backcrossing with one of the parentals can introduce genetic variation and subsequently niche differentiation, allowing for the colonization of new areas, including severe habitats (Avise 2008).

Together, hybridization and polyploidization generate unique combinations of genetic variation in parthenogenetic species, which can then be sorted according to two primary hypotheses that provide genomic explanations for the pervasiveness of geographical parthenogenesis. Both of these hypotheses assume that parthenogenetic species consist of multiple, genotypically distinct clones, which is supported by findings for several parthenogenetic vertebrates, such as *Lepidodactylus lugubris* (Murakami & Hayashi 2019). The general-purpose genotype (GPG) hypothesis

Table 2 Case studies of vertebrate asexual species exploring ecological niches using ecological niche modeling

Asexual type	Family	Geographic location	Progenitor species (maternal listed first)	Asexual species	Ploidy level	Habitat type	Main conclusions	Reference
P	Gekkonidae	Continental Australia	*Heteronotia binoei* races	*Heteronotia binoei* complex (3N1 and 3N2)	3N	Woodlands, grasslands, and disturbed habitats (open and dry)	TPs have a broader geographic distribution than PS do, but their environmental niche is narrower; TPs occupy a harsher environment than PS do; geographic parthenogenesis is supported.	Kearney et al. 2003
							Phylogeographic and biophysical distribution modeling revealed past range expansion events eastward across the arid zone.	Strasburg et al. 2007
P	Lacertidae	Caucasus and adjacent regions	*Darevskia raddei* × *Darevskia rudis*	*Darevskia unisexualis*	2N	Rocky and stony areas and high steppe habitat	Hybridization events occurred in the northeast of the Caucasus region; TP shifted habitat from PS.	Freitas et al. 2016
			Darevskia mixta × *Darevskia valentini*	*Darevskia armeniaca*	2N	Mountain forest, meadow, steppe, and disturbed habitats	TPs occupy intermediate niche relative to that for PS.	Petrosyan et al. 2019
			Darevskia mixta × *Darevskia portschinskii*	*Darevskia dahli*	2N	Sub-alps, forest, and meadow	TP climatic niche is narrower than that for PS, but geographic range is broader.	Tarkhnishvili et al. 2010
G	Ambystomatidae	Northeast United States	*Ambystoma jeffersonianum* × *Ambystoma texanum*	*Ambystoma jeffersonianum* complex	2N to 5N	Floodplain and upland forest floor habitats	Asexuals and PS have significantly different niches; geographic parthenogenesis is supported.	Greenwald et al. 2016
G	Poeciliidae	Southeast United States, Mexico, and Central America	*Poecilia latipinna* × *Poecilia mexicana*	*Poecilia formosa*	2N/3N	Waterbodies (small ditches to shallow areas in major streams)	Asexual niche overlaps with PS niche but is distinct.	Costa & Schlupp 2010

Abbreviations: G, gynogenesis; P, parthenogenesis; PS, progenitor species; TP, true parthenogen.

states that environmental tolerances vary across clones. Natural selection favors those genotypes with medium to wide tolerances that extend beyond those of sexuals, allowing the parthenogens to occupy not only the same environment as the parentals but also marginal areas out of direct competition with sexuals. The frozen-niche variation (FNV) hypothesis predicts that clonal lineages with overlapping niches with each other or with the sexual species will go extinct due to competition and that specialist clones with more distinct niches will persist (Vrijenhoek 1979, 1984). The asexual species might then consist of multiple, ecologically distinct clones, as seen in *L. lugubris* (Bolger & Case 1994). These two hypotheses are not necessarily mutually exclusive, as a parthenogenetic species might show a broad phenotype for one trait (suggestive of GPG) and a narrow phenotype for another (suggestive of FNV). Indeed, empirical ecological and genetic data from both invertebrate and vertebrate parthenogenetic species support both hypotheses (reviewed in Avise 2008, Vrijenhoek & Parker 2009).

Future research can explore the relative roles and contributions of asexual reproductive mode, hybridization, and polyploidization in driving niche evolution. In plants, polyploidization may have a more important role than reproductive mode in promoting niche divergence (Mau et al. 2015), and we can see whether similar patterns hold in parthenogenetic vertebrates.

Ecological and Historical Explanations for Geographic Parthenogenesis

Here, we discuss how the ecology and biogeography of parthenogenetic vertebrates might drive the pattern of geographic parthenogenesis. In geographic parthenogenesis, asexual species often occupy habitats distinct from those occupied by sexual species, suggesting that asexual species have evolved unique niches from their sexual ancestors. This niche evolution might be partially enabled by parthenogens' unique ecology. In many asexual species, niche evolution is constrained by the mode of reproduction. Gynogenetic and hybridogenetic species require sperm from males and must maintain some overlap with their sexual progenitors. In contrast, true parthenogens no longer require the male genome and are thus able to colonize areas without their sexual relatives. Given this, gynogenetic, hybridogenetic, and kleptogenetic species should show greater niche conservatism compared with true parthenogens, as we see in the gynogenetic Amazon molly (*Poecilia formosa*) (Costa & Schlupp 2010) and kleptogenetic mole salamanders (*Ambystoma*) (Greenwald et al. 2016) compared with parthenogenetic Bynoe's geckos (*Heteronotia binoei*) (Kearney et al. 2003) and rock lizards (*Darevskia*) (Petrosyan et al. 2019, Tarkhnishvili et al. 2010). Further, because parthenogenetic lineages do not need to interact with sexuals, they avoid the risks associated with copulation (Daly 1978), including increased predation and parasitism as seen in *Darevskia* lizards (Arakelyan et al. 2019). Fewer biotic interactions might further enable parthenogens to expand their niche and thus their distributions into marginal areas, particularly when coupled with their high reproductive rate (twofold demographic advantage; see **Figure 1**). Across studies of asexual vertebrates, we find evidence for both niche divergence and conservatism (**Table 2**), depending on both asexual reproductive mode and hybrid origin. Future studies can integrate ecological niche modeling and field sampling to determine how often geographic parthenogenesis follows from niche differentiation.

The biogeographic history of most vertebrate parthenogens might also explain the commonness of geographic parthenogenesis. Our best understanding of the evolutionary history of vertebrate parthenogenesis comes from phylogeographic studies that have integrated both population genetic data and ecological niche models. These studies show that during the Pleistocene, climate cycles led to secondary contact between genomically divergent sexual species, resulting in the hybridization events that established multiple asexual lineages. During the interglacials, novel habitat formed that then allowed the expansion of parthenogens (Kearney 2005), as seen in the

parthenogenetic Australian gecko *H. binoei* (Strasburg & Kearney 2005, Strasburg et al. 2007) and *Darevskia* rock lizards (Freitas et al. 2016, Ryskov et al. 2017) (**Table 2**). Moving forward, we can build on these foundational studies to understand the genomic basis of geographic parthenogenesis by correlating genome-wide patterns of variation with environmental data; such studies will then also allow us to predict the fate of parthenogenetic lineages under changing climates (e.g., as has been done in sexual vertebrate species; Bay et al. 2018).

HIGH-THROUGHPUT SEQUENCING OPENS OPPORTUNITIES

Each advance in high-throughput sequencing opens opportunities to pursue persistent questions about the evolution, ecology, and genomics of parthenogenetic squamates. From an evolutionary perspective, high-throughput sequencing allows researchers to genotype hundreds of individuals, providing the genome-scale data necessary to (*a*) identify parental ancestors, (*b*) quantify and compare mutation and substitution rates between asexuals and sexuals, (*c*) examine gene regulation such as dosage compensation with transcriptomes, (*d*) measure selection efficiency in parthenogenetic lineages, and (*e*) estimate the ploidy level of morphologically identical diploid and polyploid parthenogens. Further, long-read sequencing technology is becoming both cheaper and more accurate (Amarasinghe et al. 2020). These reads are essential for obtaining phased data from hybrid individuals, particularly in polyploid genomes, where differentiating across multiple allele copies is even more challenging. Long reads allow the generation of haplotyped whole-genome sequences, which in turn allow the quantification of recombination rates, TE accumulation, and larger segmental mutations. Long-read sequencing technology can also be used for Iso-Seq, or the sequencing of an entire messenger RNA with a single read, which improves our ability to quantify ASE (Wang et al. 2020). Further, approaches for methylation-sensitive sequences, such as bisulfite sequencing and chromatin immunoprecipitation sequencing, provide opportunities to study epigenetic patterns, dynamics, and inheritance in clonal systems.

CONCLUSION

Our review highlights the abundance of hypotheses and theory regarding the evolution of asexual reproduction and argues that we are poised to test these ideas using vertebrate parthenogens. With ever-advancing genome technologies and ecological tool sets, we now have the opportunity to understand the complexities of asexual vertebrate genomes and to tease apart the relative roles of mutation (including TEs), recombination, and gene conversion in shaping genomes in the absence of sex. More studies are needed that integrate genomics, epigenetics, and ecology to understand the distributions of parthenogens in vertebrates and invertebrates alike. A comprehensive picture of asexual reproduction as a null model will provide a foundation for understanding the ecology and evolution of sex in natural populations.

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