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Patterns and Processes of Diploidization in Land Plants

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Abstract

Most land plants are now known to be ancient polyploids that have rediploidized. Diploidization involves many changes in genome organization that ultimately restore bivalent chromosome pairing and disomic inheritance, and resolve dosage and other issues caused by genome duplication. In this review, we discuss the nature of polyploidy and its impact on chromosome pairing behavior. We also provide an overview of two major and largely independent processes of diploidization: cytological diploidization and genic diploidization/fractionation. Finally, we compare variation in gene fractionation across land plants and highlight the differences in diploidization between plants and animals. Altogether, we demonstrate recent advancements in our understanding of variation in the patterns and processes of diploidization in land plants and provide a road map for future research to unlock the mysteries of diploidization and eukaryotic genome evolution.

Contents

INTRODUCTION

A major insight from two decades of sequencing plant genomes is that most are not simply diploid but are diploidized paleopolyploid genomes. Although it has long been recognized that many contemporary plants are polyploids (8, 109, 163, 178), or species with duplicated genomes, comparative genomic analyses were required to provide conclusive evidence that plants experienced cycles of polyploidy followed by diploidization (4, 79, 89, 124, 169, 172, 177). Over the past century (10, 97, 176), we have learned a lot about polyploidization, but we know comparatively little about the mechanisms and forces that drive diploidization (40, 177). In the most basic sense, diploidization is the return of a polyploid genome to a diploid state (105, 160, 172, 177). One of the earliest references to this sort of diploidization was by Stebbins (161) in reference to a study by R. E. Clausen (32) on pairing behavior in *Nicotiana* allopolyploids (see also 163). (The fungal literature used the term diploidization in a different manner, e.g., 54.) The restoration of bivalent chromosome pairing behavior and associated diploid genetics is considered a key feature of diploidization. As recognized early on (161), the characteristics of a given whole-genome duplication (WGD) event impact the pairing behavior, genetics, and subsequent course of diploidization in a polyploid genome. Thus, all polyploid species do not necessarily experience the same processes of postpolyploid genome evolution and diploidization.

Bivalent: a pair of homologous chromosomes aligned on the meiotic spindle during meiosis I

Cytological diploidization: the process of chromosomal evolution and restoration of bivalent pairing and disomic inheritance following polyploidy

Genic diploidization/fractionation: the process of gene removal and loss following polyploidy by molecular mechanisms such as pseudogenization and gene deletion by recombination

Although many mechanisms of genome evolution contribute to diploidization, it can be broadly described as involving two major and largely independent processes: cytological diploidization and genic diploidization/fractionation (101, 105). Cytological diploidization occurs via sequence divergence, chromosomal rearrangements, fission, fusion, and other large-scale chromosomal evolution events that produce significant changes in genome structure and eventually lead to diploid-like chromosome pairing behavior during meiosis (101). During fractionation, many genes duplicated during the WGD event are lost, and only a subset of genes are retained as paralogs over time (53, 86). These two processes occur largely independently of each other and at different rates, yielding a diversity of genomes with different patterns of diploidization following polyploidy across lineages (104, 127, 177).

In this review, we discuss the different aspects of diploidization and postpolyploid genome evolution. We largely focus on genome evolution in the land plants but also compare their patterns and processes of diploidization to those in animals and other eukaryotes. We begin with an introduction on the nature of polyploidy and how it may affect chromosome pairing behavior during meiosis. This includes a new survey of the plant cytological literature to assess the distribution of bivalent pairing among contemporary polyploid species. In the following sections we

describe cytological and genic diploidization and summarize current knowledge on the molecular mechanisms of these distinct diploidization processes. We also review differences in the rates of diploidization in plants and present new analyses on the rates of gene loss across land plants. Finally, we highlight the growing importance of developing new models and simulations to rigorously test hypotheses on diploidization as we try to understand the fundamental question: why diploidize at all?

THE NATURE OF POLYPLOIDY AND CHROMOSOME PAIRING BEHAVIOR

A key milestone during diploidization is establishing bivalent chromosome pairing during meiosis (177). Bivalent pairing is important because it is a precursor to restoring diploid-like genetics with two alleles per locus (i.e., disomic inheritance). Although polyploids are often imagined to have multivalent pairing, many polyploid species actually have bivalent pairing at formation or evolve it quickly (166). Differences in pairing behavior are often used to distinguish the two major categories of polyploid species, allopolyploids and autopolyploids (8, 127, 138, 139). Distinguishing allo- and autopolyploids by pairing behavior is considered to be the genetic classification of polyploid species (8, 42, 43). In allopolyploids, divergence between the parental taxa is expected to limit pairing among the homoeologous chromosomes, and the homologous chromosomes are expected to form pairs of bivalents during meiosis. In contrast, autopolyploids are expected to have homologous chromosomes that form either bivalents or multivalents (**Figure 1**). The bivalent pairing expected to occur in allopolyploids should lead to mostly disomic inheritance (i.e., two alleles at each of two distinct loci), whereas autopolyploids are expected to have multisomic inheritance (i.e., multiple alleles at a single locus) (**Figure 1**). It is important to point out that even though strictly bivalent pairing can occur in some autopolyploids, random segregation of homologous chromosomes during meiosis can result in multisomic inheritance (66, 76, 83, 137, 164). Therefore, multisomic inheritance is a unique feature that can define autopolyploids (129, 166). Although the genetic definition is widely used in the field, many studies distinguish allo- and autopolyploid species by a taxonomic definition that emphasizes the number of progenitor species (139). Allopolyploid species result from the hybridization of two or more species with genome duplication. In contrast, autopolyploids result from a genome duplication within a single progenitor species (8, 42). The taxonomic definition putatively gets around one of the limitations of the genetic definition: change in pairing behavior over time. As polyploid species diploidize, bivalent pairing and disomic inheritance are restored. This means the genetic classification of an allo- or autopolyploid may be contingent on the age of the polyploid species. The taxonomic definition captures the nature of polyploid species regardless of the age of the WGD event and stage of diploidization.

Although the definitions of allopolyploidy and autopolyploidy are straightforward, in practice it is often difficult to describe the nature of polyploid species and degree of diploidization because of the dynamic processes of genome divergence and evolution. Allo- and autopolyploidy represent two ends of a continuum of variation in subgenome divergence and independence (8, 139, 161). This gradient of polyploid variation has long been recognized (161, 163). For example, the term segmental allopolyploidy was used for polyploid species that show mixtures of bivalent and multivalent formation (161). Differences in observed pairing behavior across this spectrum have been documented in multiple systems (139). This variation led to describing the inheritance patterns of segmental allopolyploids and other polyploids in the middle of this gradient of pairing behavior as being mixosomic (160). Although segmental allopolyploidy and mixosomic inheritance can be recognized by careful genetic analyses, most studies simply classify polyploid species as allo- or

Disomic inheritance: regular pairing and segregation of two chromosomes that produce two alleles at a locus

Multivalent: three or more homologous chromosomes aligned on the meiotic spindle during meiosis I

Homologous chromosomes (homologs): a set of chromosomes that pair up during meiosis I; in each pair, one is of maternal origin and the other of paternal origin

Homoeologous chromosomes (homoeologs): a set of chromosomes in an allopolyploid that are derived from different parental species and have shared homology

Multisomic inheritance: combinations of chromosome pairing and segregation that yield more than two alleles at a locus; also known as polysomic inheritance

Allopolyploidy: polyploid species formed by interspecific hybridization and whole-genome duplication; generally considered to have pairs of homologous chromosomes from each parent that form bivalents during meiosis

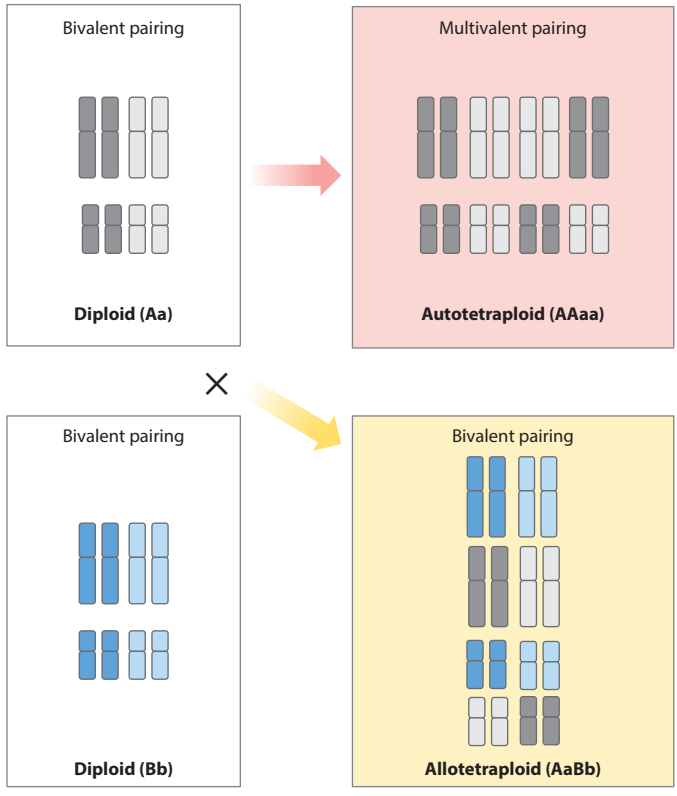

Figure 1

Illustration of chromosome pairing behavior during meiosis in a diploid (*white*), autotetraploid (*pink*), and allotetraploid (*yellow*). Chromosomes that are the same size but different shades of the same color represent homologous chromosomes. Chromosomes of the same size but in different colors (i.e., *blue* versus *gray*) represent homoeologous chromosomes.

Autopolyploidy: polyploid species with a single progenitor species; typically expected to have sets of homologous chromosomes that form multivalents during meiosis

Segmental allopolyploidy: polyploid species with a mixture of bivalent and multivalent chromosome pairing

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autopolyploids without distinguishing the polyploid variation continuum (8). However, to understand diploidization we ultimately must grapple with this continuum of variation and recognize that not all studies of postpolyploid genome evolution are examining the same biology. For example, if a polyploid species is born with diploid-like bivalent pairing and disomic inheritance, is the ongoing divergent evolution of those homoeologous chromosomes really diploidization? Is it equivalent to the evolution of bivalent pairing in a multivalent autotetraploid? Analyses of diploidization in recent and ancient polyploid genomes need to better understand the origin of the species to evaluate what is and is not due to diploidization in these genomes.

One starting point to understand diploidization in polyploid genomes is to assess how many contemporary polyploid species have bivalent pairing and how this pattern aligns with allo- and autopolyploid species. To address this gap in our knowledge, we conducted a survey of pairing behavior in allo- and autopolyploid species recognized by the taxonomic definition. The initial survey was based on a previous study of the frequency of allo- and autopolyploidy that examined data for 4,003 species from 47 genera of vascular plants (8). For each species, we recorded the chromosome pairing behavior during meiosis from the cytological literature (**Supplemental Table 1**). We classified the meiotic chromosome pairing behavior as either strictly bivalent pairing (only bivalent formation was observed) or a mix (multivalent or a mixture of bivalent

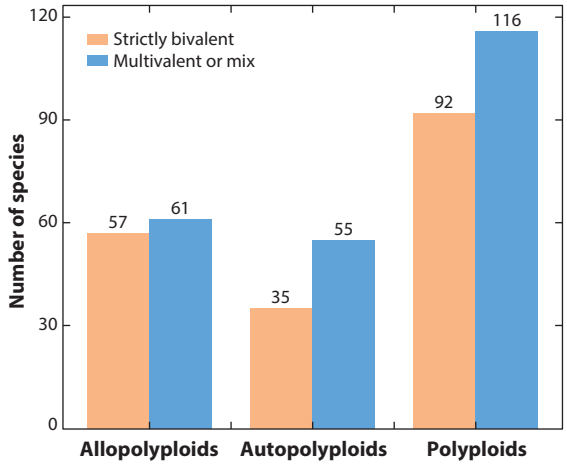

Figure 2

The frequency of strictly bivalent (*orange*) versus multivalent or a mix of bivalent and multivalent pairing (*blue*) and whether species are reported as allo- or autopolyploids. This meta-analysis is based on 208 species (**Supplemental Table 1**). Pairing behavior was not significantly different between allo- and autopolyploids (Fisher's exact test $p = 0.2054$). The categories represent allopolyploids, autopolyploids, or all polyploids combined. The y-axis represents the number of species. Data from Barker (7).

Supplemental Material >

and multivalent pairing). We identified 208 polyploid species from 40 genera (**Supplemental Table 1**) with at least one record of meiotic chromosome pairing behavior (**Figure 2**). Although it would be optimal to include more than one observation of pairing behavior per species, most historical cytological analyses do not report the frequency of the chromosome pairing behavior occurrence and include only a single observation. Among these studies, 118 were classified by Barker et al. (8) as allopolyploids and 90 as autopolyploids (**Figure 2**; **Supplemental Table 1**). Overall, we found that 92 of these species had strictly bivalent pairing, whereas 116 had mixed or multivalent pairing. Among species classified as allopolyploids, 48.3% had bivalent pairing and 51.7% had at least some multivalent formation during meiosis. Only 38.9% of the autopolyploids had bivalent pairing and 61.1% of the autopolyploids had multivalent or mixed pairing behavior. Consistent with our expectations, we found a lower frequency of strictly bivalent pairing among autopolyploid species compared to allopolyploids. However, the difference in pairing behavior between allo- and autopolyploids was not significantly different (Fisher's exact test $p = 0.2054$). This result may be due to the taxonomic and phylogenetic classification of allo- and autopolyploid species used by Barker et al. (8), but the methodology used to classify polyploid species in that study is consistent with the approaches used broadly in the community. The distribution of pairing behaviors suggests that segmental allopolyploidy may be prevalent among polyploid plant species and that bivalent pairing may evolve rapidly in many autopolyploid species.

Despite possessing twice the number of chromosomes as their progenitors, and regardless of the taxonomic nature of polyploid speciation, nearly half (44.2%) of the polyploid species we surveyed had bivalent chromosome pairing behavior. As expected, allopolyploid species demonstrated more strictly bivalent pairing than autopolyploid species. The stable meiosis of allopolyploid species likely results from pairing preferences for homologs with highly similar and collinear sequences and suppression of pairing between the divergent homoeologs (33, 72, 127, 139). Future studies need to determine whether and to what degree sequence and structural divergence among homoeologous chromosomes lead to bivalent formation in polyploids. Further analyses

Mixosomic inheritance: the combination of disomic and multisomic inheritances in a species

on the degrees of sequence and structural divergence of the parental diploids and the pairing behavior of their allopolyploid species would provide some insight into this question. Similarly, analyses of the age of the surveyed autopolyploid species would help explain why nearly 40% had strictly bivalent pairing. Are these species simply older autopolyploids compared to species with more frequent multivalent pairing? Or are they cryptic allopolyploids that were misclassified as autopolyploids? The answers to these questions will help us understand the mechanisms that lead to the restoration of bivalent pairing in allo- and autopolyploids and, eventually, the evolution of disomic inheritance across the spectrum of polyploid species.

MECHANISMS OF CYTOLOGICAL DIPLOIDIZATION

What are the mechanisms that lead to the restoration of bivalent pairing, disomic inheritance, and cytological diploidization of polyploid genomes in plants? Although the forces and mechanisms driving cytological diploidization are not completely understood (50, 72, 85), the process broadly involves sequence divergence and changes in genome organization that ultimately produce pairs of homologous chromosomes that pair with each other and limit homoeologous pairing (**Figure 3**). These changes include chromosomal rearrangements, fissions, fusions, and other reorganizations that lead to differentiated pairs of homologous chromosomes (85, 152). Dysploidy can also occur as a part of genome evolution associated with cytological diploidization, causing changes to base chromosome numbers (48, 105) and chromosome loss following WGD (99, 103, 106, 152, 183). More broadly, it is not yet clear if these changes accumulate (neutrally or through local adaptation) and lead to divergent resolution in different populations of a polyploid species (174), or if natural selection is driving cytological diploidization because of some fitness benefit of diploid genetics or meiosis.

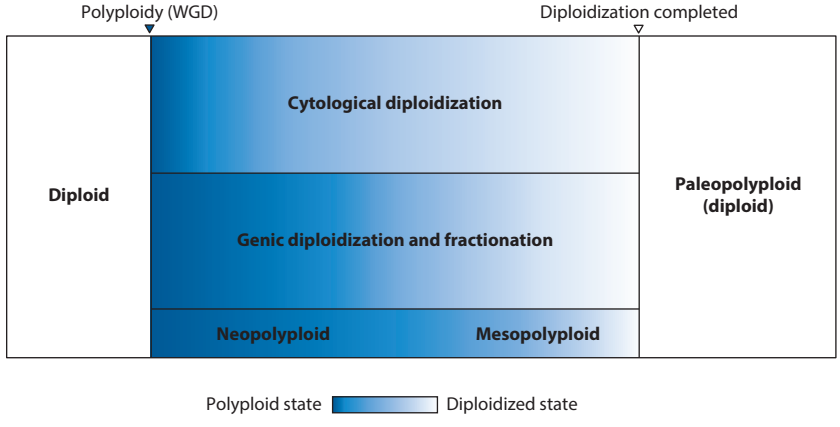

Figure 3

The major processes and mechanisms of diploidization. From left to right, the abrupt transition from white to blue represents a change from diploidy to polyploidy. The gradual transition from blue to white represents diploidization. The shade of color shows the hypothetical level of diploidization. The differences in shade of color between cytological and genic diploidization show that they are independent processes that occur at different rates. The process of cytological diploidization involves chromosomal evolution leading to the restoration of bivalent pairing and disomic inheritance following polyploidy. The process of genic diploidization and fractionation involves gene removal and loss following polyploidy by molecular mechanisms such as pseudogenization and gene deletion by recombination. Abbreviation: WGD, whole-genome duplication.

Evidence from studies of established polyploid species indicates that natural selection is likely driving some aspects of cytological diploidization. Research on established polyploids suggests they have lower crossover frequencies compared to neotetraploids or their diploid relatives (139, 184). Recently formed polyploid species, especially autopolyploids but many allopolyploids as well (**Figure 1**), produce multivalents during meiosis. Multivalents are generally less stable during meiosis than bivalents and can lead to the loss of chromosomes during anaphase (85, 183, 187). This loss of chromosomes and other challenges of multivalent pairing and segregation can lead to reductions in fitness. These observations lead to a hypothesis that selection may reduce the number of crossovers or chiasma to suppress multivalent formation and nonhomologous pairing in polyploid species (20, 29, 85). Reducing the number of crossovers limits the opportunity for chromosomes to pair with more than one partner during meiosis and leads to more stable, bivalent pairing.

In autopolyploids, meiotic stability is associated with the rate of crossover (19). More meiotically stable autopolyploids have diploid progenitors with lower frequencies of crossover formation, whereas polyploids with higher multivalent frequencies are formed by diploids with higher crossover rates (19, 70, 115). Studies suggest a single crossover per pair of homologous chromosomes is essential in most diploid species for chromosome segregation (36, 80). For a chromosome to be associated with more than one partner during meiosis, at least two crossovers are required (19). Theoretically, reducing crossover to one per pair of homologous chromosomes in autopolyploids would be ideal for chromosome segregation and lead to bivalent formation (20). A model has been proposed for the mechanistic basis for limiting the number of crossovers in autopolyploids (20). In this model, the number of crossovers is reduced to one if the range of crossover interference needs to be larger than the distance to the end of the chromosome. Although the genetic and molecular mechanisms that control the number of crossovers are not well understood, progress is being made in understanding the genetic basis of autopolyploid meiosis in autotetraploid *Arabidopsis arenosa* (73, 114, 184). Previous studies used population data to show that eight unlinked candidate genes were important for meiotic chromosome pairing (73, 184). Strong signatures of selective sweeps are found on these genes, and they are differentiated between polyploids and diploids. The results suggest that the genetics of reestablishing bivalent pairing in autopolyploid meiosis is likely to be polygenic (184). A more recent follow-up study has identified the derived alleles of two genes, *ASY1* and *ASY3*, that are associated with meiotic changes in *A. arenosa* (114). This functional study also found that derived alleles of both genes are associated with traits in meiosis, such as reduction of multivalent formation, reduced chromosome axis length, and a tendency of more rod-shaped bivalent formation during meiosis (114). This work provides the first empirical analysis of multiple genes involved in bivalent restoration in autopolyploid meiosis and provides evidence that pairing behavior in autopolyploids can be genetically controlled. Although this model of restoring bivalent pairing has been developed in the context of autopolyploid species, it likely applies to many allopolyploids that experience multivalent pairing as well (**Figure 2**).

Meiotic chromosome pairing behavior in allopolyploids is traditionally considered to be stable and diploid-like (33, 127, 139). The general explanation of the stable meiosis in allopolyploid species is that the homoeologous chromosomes are already differentiated, making it easier to establish bivalent pairing between homologs and suppress homoeolog pairing (33, 127, 139). Although the molecular mechanism of how sequence and structural divergence of chromosomes influence pairing remains unclear (21, 34, 85), many allopolyploid species still experience significant chromosomal change following genome duplication. Extensive chromosomal rearrangements and chromosome losses have been found in both synthetic *Brassica napus* and natural populations of *Tragopogon miscellus* (28, 183). As we found above (**Figure 2**), many allopolyploids also demonstrate some multisomic pairing and need to at least partially restore bivalent pairing to diploidize.

Studies have shown that the restoration of diploid-like chromosome segregation is genetically controlled (50, 60, 72, 107, 144). The best-known example is the *Ph1* locus, which has been studied in grasses, especially in wheat. This locus is associated with suppressing homoeologous pairing and promoting homologous chromosome pairing in meiosis. In the absence of *Ph1*, the number of crossovers increases and extensive homoeologous pairing can occur (147). Loci with similar effects have also been identified in allotetraploids *B. napus* (77, 96) and *Arabidopsis suecica* (71). A recent study proposed a mechanism for suppression of nonhomologous crossovers in allopolyploids (60). The gene *MSH4* is essential for the main crossover pathway in *B. napus*. The number of nonhomologous crossovers decreases if *MSH4* returns to a single copy, and these crossovers will not be affected if *MSH4* is lost. Significantly, they found a convergent pattern of *MSH4* returning to a single copy following multiple independent WGDs across the angiosperms. However, researchers suggest *MSH4* is unlikely to contribute to meiosis stability in autopolyploids because it mainly affects nonhomologous crossovers that are not thought to be important in autopolyploid pairing. This study provides a new mechanism for the restoration of bivalent pairing in allopolyploids and suggests that chromosome pairing in allopolyploids is genetically determined across flowering plants (60).

Overall, the mechanisms behind restoring bivalent pairing and disomic inheritance are still not fully understood (50, 72, 85). Some evidence suggests that chromosome pairing is genetically determined in different auto- and allopolyploid systems (71, 77, 96, 184). Few systems have been studied to understand the cytological diploidization of autopolyploids (21, 73, 114, 184). It remains to be studied how these mechanisms may vary across the phylogeny (21, 73, 114, 184). The recent study on *MSH4* suggests that at least some of the molecular mechanisms for restoring bivalent pairing are potentially broadly shared across flowering plants (60). Future studies should look for *MSH4* and other genes associated with pairing and test whether chromosome pairing is genetically determined across land plants. Beyond the genetics of bivalent pairing, the accumulated empirical evidence has also shown that chromosomal changes such as rearrangement, translocation, and chromosome loss occur during diploidization (85, 99, 103, 106, 152, 183). Chromosomal evolution could lead to sequence divergence by introducing gene deletions or duplications and by changing the positions of recombination hotspots that lead to differential rates of sequence divergence (78, 118, 121). A recent study using autopolyploid *Arabidopsis thaliana* lines highlights the complexity of different forces that may influence pairing in polyploids. Crosses within and between synthesized *A. thaliana* Col and Ler lines were used to explore chiasma formation and pairing in autopolyploids (130). A significant excess of bivalent pairing in these crosses was observed for chromosomes 2 and 3. Notably, chromosome 3 has a relatively large inversion between Col and Ler, and other sequence and structural divergence may play a role in driving higher bivalent pairing on these chromosomes (130). Future investigations such as this are needed to understand how the interactions among sequence similarity and chromosomal structure ultimately reduce homoeologous pairings and drive the restoration of bivalent pairing and disomic inheritance.

GENIC DIPLOIDIZATION AND FRACTIONATION

Although some polyploid species are essentially cytologically diploid at birth with bivalent pairing, most polyploid genomes go through extensive gene loss and fractionation. Plant genomes are highly dynamic with significant turnover in content, especially following WGDs (9, 149, 160, 172). All genes are duplicated during polyploidization, and many of these new paralogs do not persist for long (1, 11, 35, 41, 156). This process of gene removal and loss following polyploidy is known as fractionation (53, 86). Although fractionation does not necessarily lead to the restoration of bivalent pairing or disomic inheritance, focusing on pairing behavior as the only process

involved in diploidization misses the other aspects of post-WGD genome evolution. These include significant changes in gene content, network structure, and expression (18). Fractionation is a particularly important component of diploidization and postpolyploid genome evolution because nearly all polyploids that persist experience gene loss and the resolution of duplicated gene networks.

Gene deletion by illegitimate recombination is considered to be the predominant mechanism of fractionation and genome size reduction in flowering plants (39, 52, 53, 59, 100, 128). Illegitimate recombination can occur through unequal recombination between dispersed homologous regions (65). This asymmetric pairing followed by unequal sequence exchange can result in gene duplication or deletion (6, 63, 175). Illegitimate recombination can also occur via intrachromosomal recombination and is characterized by flanking direct repeats, which are the products of circular recombination and excision that result in gene deletion (84). Many apparent gene deletions in plant genomes are flanked by direct repeats, suggesting that illegitimate recombination was involved (155, 165, 170, 180). Studies have also found that illegitimate recombination can occur between homoeologs in allopolyploids, resulting in deletions (55) and gene conversion (94). Possibly related to fractionation, illegitimate recombination is considered to be the primary mechanism for transposable element (TE) removal, with similar flanking direct repeats as a classic signature of excised TEs (13, 39, 69, 140, 168). Variation in the presence of active TE families in plant genomes could impact gene loss and fractionation (179). TEs are often silenced by methylation, but this also reduces the expression of neighboring genes (74). This attenuation of neighboring gene expression may lead to selection to eliminate these TEs while increasing the chance that nearby genes could be deleted (26, 179). Gene deletion by errors in recombination, involving TEs or not, appears to play a significant role in gene fractionation following WGDs.

What about areas of the genome that experience low recombination rates? Gene loss in regions of relatively low recombination has only recently been studied in plant genomes. Unlike areas of genomes that experience high recombination, in areas of low recombination, genes may persist and accumulate deleterious substitutions. This accumulation of mutations could lead to a higher frequency of pseudogenization in these areas. In contrast to fractionation caused by illegitimate recombination, pseudogenes are not physically deleted from the genome and may persist for long periods of time after nonfunctionalization (181, 182, 189). Pseudogenes are often considered to be relatively rare in plant genomes (27, 45, 47, 53, 142, 149), but they are poorly characterized for a clade with a high frequency of duplication events. A recent study sought to better characterize pseudogenes in plant genomes and estimated that the number of pseudogenes is highly lineage-specific in angiosperm genomes, ranging from 5,000 to over 73,000 (182). These results suggest that pseudogenization may be more common in plant genomes than previously thought. As expected, a deeper analysis in a few genomes with recombination data, in particular soybean, found that pseudogenes were enriched in low recombination areas near centromeres (182). Thus, variation in recombination rates and genomic locations may significantly influence the mechanism of genic diploidization in plant genomes. Improved recombination maps for more plant genomes and better characterization of pseudogenes are needed to explore this relationship further.

In many plant genomes, fractionation has also been observed to be nonrandom (22, 58, 131, 171). This biased fractionation can result in subgenome dominance in which one subgenome is retained more than the other. This phenomenon has been widely observed across angiosperm lineages (27, 45, 47, 53, 142, 149). In general, genes from the more highly retained subgenome are expressed at a higher level than their homoeologs (27, 149). One possible mechanism that could drive this subgenome dominance is the distribution of TEs in each subgenome. Methylation of TEs reduces the expression of the TE itself but may also decrease the expression of nearby genes (74, 75). In allopolyploids, one parental genome may have a higher TE density and higher level of

methylation compared to the other parental genome. Researchers have hypothesized that genes from the subgenome with higher TE density and methylation may be expressed at a lower level, resulting in more fractionation compared to the other subgenome (179). Under this hypothesis, there is more opportunity for subgenome dominance to occur with allopolyploid species (179). This hypothesis has also been extended to paleopolyploidy events (56). It has been proposed that genomes with evidence of biased fractionation and subgenome dominance are more likely to be ancient allopolyploids (56). However, studies have shown that allopolyploid genomes do not always demonstrate subgenome dominance. For example, in allopolyploids such as *B. napus*, wheat, and cotton, subgenome dominance is not observed (25, 64, 132, 185). In soybean, subgenome dominance is not found, and the nature of its paleopolyploid event is still unresolved (190). These observations suggest that the degree of genome differentiation prior to polyploidy may determine the amount of subgenome dominance. It remains to be studied why this pattern varies across the phylogeny. Recent studies have provided progress on understanding the potential mechanisms that may drive subgenome dominance and biased fractionation. In the lotus genome, researchers found that subgenome dominance and biased fractionation are associated with higher gene body methylation, degree of protein-protein interactions, and gene expression levels (157). Recent studies also suggested homoeologous exchanges in allopolyploidy are likely to impact the pattern of subgenome dominance (3, 17, 46, 55). The phylogenetic distribution and relative contributions of these mechanisms to the evolution of subgenome dominance and biased fractionation are not yet clear, but additional analyses leveraging population genomics and resynthesized polyploids as well as other analyses of genetics and fitness will provide further insight into their roles in the polyploid genome evolution.

The drastic and biased gene loss that accompanies diploidization can also result in significant genome reorganization, which may occur to resolve genomic conflicts or dosage balance issues that would otherwise reduce polyploid fitness (134, 172). It has been shown that paralogs with more interaction partners, such as transcription factors, are more likely to be retained following WGD to maintain protein product stoichiometry or dosage (38, 51, 167). This dosage balance hypothesis (DBH) also predicts that dosage-sensitive genes will be preferentially lost following small-scale gene duplication events to prevent dosage disruptions, as their interaction partners are not doubled (15, 38, 51, 91). An alternative to the DBH attributes retention of paralogs to functional diversification, especially neofunctionalization (i.e., a gene copy acquiring a novel function) (123) or subfunctionalization (i.e., each gene copy retaining part of the original function) (98). A previous study suggests that subfunctionalization may also drive cytological diploidization by maintaining appropriate chromosome pairs and promoting bivalent chromosome pairing and disomic inheritance (85). However, neo- and subfunctionalization cannot explain the parallel pattern of gene retention following different WGDs (11, 37, 104). Among these hypotheses for duplicate gene retention (51, 81), the DBH is the only hypothesis that explicitly predicts the parallel retention and loss of functionally related genes across species following WGD (35, 51, 167). A recent study of tandem duplicate genes in mammals suggests that the DBH might explain the initial survival of these gene duplicates and neo- or subfunctionalization may be more important for the long-term retention of paralogs (82). It remains to be understood what determines the portion of retained duplicate genes that are explained by the DBH, neo- and subfunctionalization, and other processes, and how this pattern varies across different lineages of plants.

In general, genic diploidization/fractionation occurs after all WGDs. Although the complete set of forces and mechanisms that drive fractionation are not yet understood, there is plenty of evidence that the process is generally not random with regard to the subgenomes and types of genes that are retained and lost (22, 58, 131, 171). Future studies should aim to better understand how much fractionation is determined by the nature of polyploidy or other factors such as level

of methylation in parental genomes. We also need to understand how genic diploidization and fractionation contribute to resolving genomic conflicts or dosage balance issues. This will help improve our understanding of the fate of duplicate genes from WGD. Given that diverse mechanisms and forces appear to drive fractionation, the processes of genic diploidization may vary considerably among lineages.

RATE OF DIPLOIDIZATION IN PLANTS

The processes of diploidization involve many mechanisms and forces, and it is not yet clear how they operate in different lineages of plants. Most studies on genetic and cytological diploidization have focused on the angiosperms. In *Tragopogon*, it has been shown that the parallel pattern of gene loss and chromosomal rearrangements can be established in only 40 generations (23). Similarly, Xiong et al. (183) studied 10 generations of the resynthesized allopolyploid *B. napus* and found evidence for many chromosomal rearrangements and aneuploidies. Although there is evidence for rapid chromosomal evolution following polyploidy, a recent study demonstrated that the rate of diploidization following WGD can vary among related lineages (104). In 13 independent Brassicaceae mesopolyploidies, multiple species displayed different degrees of diploidization yielding a range of chromosome numbers and rearrangements across lineages. The different levels of diploidization are not clearly predicted by the age of these polyploidy events (104). More striking, in a recent cytological study of a Brassicaceae tribe largely endemic to Australia, different lineages descending from a common allopolyploid ancestor can have different rates of diploidization (106). The difference in rate is mainly driven by the number of chromosomal rearrangements observed in each species (106). Given that the rate of diploidization can vary dramatically in the descendants of a single WGD, the rate of diploidization likely varies across different lineages of flowering plants. However, it is not yet clear how much the rates of different aspects of diploidization vary across the land plant phylogeny, and the forces driving these differences in rate are still unknown.

Relatively little is known about diploidization outside of angiosperms. A recent study in *Sequoia* confirms that an autopolyploidization event occurred around 33 Mya (153). However, *Sequoia* has apparently maintained multivalent pairing since this paleopolyploidy (162), suggesting a slow diploidization process in comparison to flowering plants (153). Although they are debated (146, 191), genomic analyses have inferred at least three other ancient WGDs in the gymnosperms (89, 90, 124). Other recent studies have found evidence of neopolyploidy in *Ginkgo* (158, 159) and *Juniperus* (49). These ancient and recent WGDs provide opportunities to estimate the rate of genic and cytological diploidization in gymnosperms. Better understanding of diploidization in gymnosperms may provide a new angle to understand why polyploidy is relatively rare in most of the gymnosperms (2). As in the gymnosperms, diploidization remains to be studied in ferns. It has been hypothesized that ferns experienced multiple rounds of ancient WGDs without losing their chromosomes (12, 67, 68). In contrast to the flowering plants, diploidization in the ferns has been hypothesized to be predominantly driven by gene silencing or pseudogenization rather than by gene deletion (7, 67, 119, 120). A few studies have identified multiple silenced copies of nuclear genes in putatively diploid homosporous fern genomes (110, 111, 133) and the active process of gene silencing without chromosome loss in a polyploid genome (57). Unlike in angiosperms, chromosome number and genome size are correlated in ferns (7, 30, 119), and there is evidence of constraint on average chromosome size (95). However, the molecular mechanism of gene fractionation and the rate of diploidization in ferns are still unknown. Two heterosporous fern genomes have been published (87), but these two genomes might experience different processes of diploidization compared to the homosporous ferns, which have much higher average chromosome numbers. Similar to diploidization in the gymnosperms and ferns, relatively little is

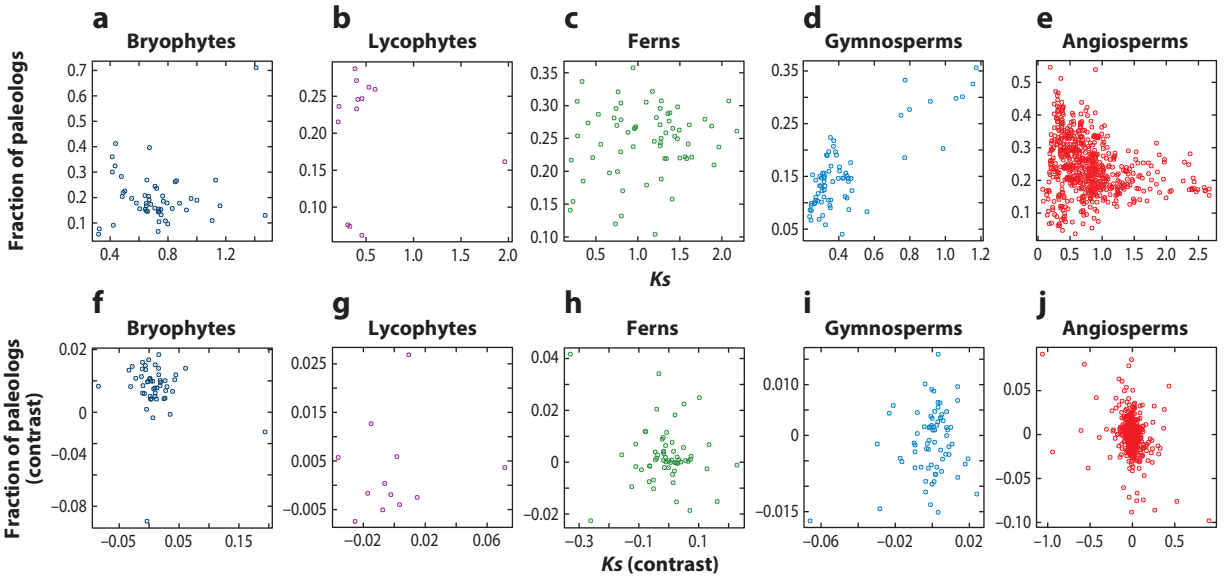

Figure 4

The fraction of genes retained from a WGD over the estimated median *Ks* value of a WGD in land plants with and without PICs. (*a–e*) The x-axis represents the *Ks* value of a WGD inferred by a mixture model in gene age distribution analysis. The y-axis represents the fraction of genes retained from a WGD, which is estimated as the number of paralogs retained from a WGD divided by the total number of unigenes of a transcriptome. (*f–j*) The phylogenetically corrected rate of post-WGD paralog loss in land plants. Both the fraction of genes retained from a WGD (y-axis) and estimated median *Ks* value of a WGD (x-axis) in land plants were corrected using PICs. This study is based on 815 species of land plants: (*a*,*f*) bryophytes, 52 species; (*b*,*g*) lycophytes, 13 species; (*c*,*h*) ferns, 66 species; (*d*,*i*) gymnosperms, 73 species; (*e*,*j*) angiosperms, 610 species (see also **Supplemental Table 2**). Abbreviations: *Ks*, synonymous divergence; PICs, phylogenetic independent contrasts; WGD, whole-genome duplication.

Supplemental Material >

known about diploidization in the other lineages of land plants. Future studies should estimate the patterns and processes of diploidization with chromosome-level genome assemblies of these lineages, especially mosses, Lycopodiaceae, Isoetaceae, and the homosporous ferns where polyploidy seems to be prominent (124).

Estimating the rate of genic and cytological diploidization in plants can be challenging because the process occurs across large timescales and requires substantial genomic data. Additional phylogenetic and cytological analyses could be used to develop greater insight into the rate of cytological diploidization (**Figure 4**). Similarly, the rate of gene loss following polyploidy can be estimated from recent studies on the incidence of paleopolyploidy across the plant phylogeny. With genomic and transcriptomic data, the rate of duplicated gene loss in ancient polyploids can be estimated by comparing the fraction of paralogs in a genome derived from a WGD and the age of the WGD across multiple events and species. In general, studies have used synteny or duplicate gene age distribution analyses to infer duplicate genes derived from the polyploidy events (61, 136, 141). The relative age of a WGD can be estimated using the synonymous divergence (*Ks*) of the paralogs in the WGD peak from a *Ks* plot. By plotting the fraction of retained WGD paralogs in the genome (% paleologs) against the median paralog divergence for a WGD, we can obtain an estimate of the variation in the rate of genic diploidization following ancient WGDs.

Previous research has found that the fraction of genes retained from WGDs decreases exponentially over time in flowering plants (61, 136, 141). To estimate variation in the rate of gene loss across land plants, we analyzed land plant transcriptomic data of 815 species that are inferred to

have at least one round of ancient polyploidy from the One Thousand Plant (1KP) transcriptomes project (124). These species were organized into five major lineages of land plants: bryophytes, lycophytes, ferns, gymnosperms, and angiosperms (**Supplemental Table 2**). We used mixture modeling to identify genes retained from the most recent ancient WGD that each species experienced based on the WGD peak in the *Ks* plot (90). The paralog divergence of the WGD was estimated by the median *Ks* value of the WGD peak. We estimated the fraction of paleologs by using the total number of genes retained from an ancient WGD divided by the total number of unigenes in the transcriptome (**Supplemental Table 2**). We then plotted the fraction of paleologs with paralog divergence (*Ks*) of the WGD for each species (**Figure 4**). To infer if there was a significant trend in the data, we fit linear and exponential models to the distribution (**Supplemental Table 3**). Consistent with previous research (136, 141), we found a decrease in the fraction of retained paleologs over time in the angiosperms (**Figure 4**; **Supplemental Table 3**). We also observed higher variation in the fraction of retained paralogs among relatively young WGDs (lower *Ks* values) compared to older WGDs (higher *Ks* values). In contrast, we observed an increase in the fraction of paleologs over time in the gymnosperms (**Figure 4**; **Supplemental Table 3**). The bryophytes, lycophytes, and ferns did not have a significant increase or decrease in the fraction of retained WGD paralogs over time (**Figure 4**).

Supplemental Material >

One issue with analyses of ancient polyploidy is that many taxa may be closely related, and some taxa may share the same ancient duplication event. To test whether there was any phylogenetic signal for the fraction of retained paralogs and the relative age of the polyploidy, we used the phylosig function in the phytools R package (143). We found evidence of significant phylogenetic signal for all categories except fractions of paleologs in the ferns and lycophytes. To address the potential impact of these closely related species and phylogenetically shared WGDs on the observed relationship between WGD age and paleolog retention, we used phylogenetic independent contrasts (PICs) to account for the phylogenetic relatedness among lineages in our dataset. Specifically, we transformed raw values of the fraction of genes retained from each WGD and *Ks* value of a WGD and the phylogeny from the 1KP project using the pic function in the ape (analyses of phylogenetics and evolution) R package (135). Similar to the results above, our phylogenetically corrected analyses did not recover a significant relationship between gene loss and the relative age of the WGD event in bryophytes, lycophytes, and ferns (**Figure 4**; **Supplemental Table 3**). The significant positive relationship observed in the gymnosperms was not significant after taking phylogeny into account (**Figure 4*i***; **Supplemental Table 3**). Our phylogenetically corrected analyses recover a significant linear fit ($p < 0.001$, adjusted R-squared $= 0.09593$, slope $= -0.04506$) and a significant exponential fit ($p < 0.001$, $b = -0.2032$) in angiosperms (**Figure 4*j***; **Supplemental Table 3**). Similar to studies that did not take phylogeny into account (136, 141), our study found that paleologs were lost over time. We found that the relative age of the WGDs explains about 10% of the variation in the amount of gene loss in the linear model fit after PICs (**Supplemental Table 3**). Our study provides the first observation of the rate of gene loss in other lineages of land plants. Unlike flowering plants, the amount of gene loss from a WGD does not appear to be correlated with the relative age of the WGDs in these lineages. Our results suggest the dominant mechanism of fractionation may vary across land plants and appears to be different in angiosperms compared to other land plants. Considering that the relative age of the WGD explained a relatively small amount of the variation in gene loss in angiosperms, other mechanisms are clearly important. It may be that each WGD ultimately experiences different patterns of fractionation. Every post-WGD lineage experiences different demography, selection pressures, and other population genetic differences that could drive unique rates of gene loss. Variation in all of these dimensions likely contributes to the differences in the patterns of fractionation that we observed across the land plant phylogeny.

Our results highlight that there is still much we do not understand about diploidization. Although other analyses also suggest that the rate of diploidization is likely to vary across the phylogeny of plants (106), it is not clear why we observed no relationship between the age of a WGD (as inferred by paralog divergence) and the fraction of retained paralogs for most clades of land plants. Future studies are needed to understand if the angiosperms have evolved novel mechanisms of gene fractionation distinct from those found in other land plants. Sample size in other lineages may contribute to some of the differences we observed, but the bryophytes, ferns, and gymnosperms were all represented by more than 50 species. Given the potential importance of eliminating genes after WGD (16, 38, 51, 167), the apparently efficient gene fractionation in angiosperms may be a part of their evolutionary success. Similarly, more comprehensive analyses of pseudogenization across land plants are needed to understand variation in gene loss among lineages. It also remains to be resolved how allo- and autopolyploidy influence the rate of gene loss and chromosomal evolution. Analyses leveraging comparative genomic approaches from emerging chromosome-level gymnosperm and homosporous fern genomes will be important to address why these rates of diploidization differ across land plants. Similarly, deeper analyses of populations and species descended from the same WGD are needed to understand the forces that drive diploidization. Our analyses and others (61, 136, 141) indicate that there is ample variation in the rates of diploidization to begin understanding these forces.

DIFFERENCES IN DIPLOIDIZATION BETWEEN PLANTS AND ANIMALS

Variation in the patterns and rates of diploidization is also evident between plants and animals. In angiosperms, most of the gene loss that occurs during fractionation is attributed to intrachromosomal recombination (53, 148, 165, 180). However, in animals many gene losses appear to be caused by pseudogenization (27, 45, 47, 53, 142, 149). Vertebrate genomes do not seem to rapidly remove functionless nonrepetitive DNA, and pseudogenes can be carried for tens of millions of years (14, 93, 112, 151).

Patterns of gene loss following paleopolyploidy have been studied in many flowering plants such as *A. thaliana* (22), *Brassica* (22, 58, 131, 171), and maize (22, 58, 131, 171), as well as more recent cotton allopolyploids (173). A general pattern that has been found across these flowering plant genomes is that most of the gene losses are due to illegitimate recombination rather than gene pseudogenization (53, 148, 165, 180). In maize, around 10% of the paleologs have been removed after a whole-genome duplication that occurred around 12 Mya. These paralogs were deleted by intrachromosomal recombination facilitated by direct repeats flanking the gene or exons (180). In *Brassica rapa*, gene loss following the Brassiceae paleohexaploidy was driven by the same gene deletion mechanism (165).

In contrast to plant genomes with rapid gene deletion caused by intrachromosomal recombination, pseudogenization appears to be the major gene loss mechanism in vertebrates (14, 93, 112, 151). The most common type of pseudogenization occurs when a gene is disrupted by mutations and becomes unexpressed or nonfunctional (188). For example, all of the nearly 200 genes lost since humans diverged from chimpanzees are present as pseudogenes in our genome (151). Another excellent example of slow gene deletion in vertebrates comes from the recently sequenced rainbow trout genome (14). Analyses of the genome revealed an ancient WGD shared by the salmonid family. After nearly 100 million years of evolution, syntenic analyses found that the two subgenomes are still highly collinear. Nearly half of the protein-coding genes are retained in the genome, and most of the gene loss is due to pseudogenization. They also estimated that the average rate of gene inactivation is ~170 genes per million years (14). Similarly, carp experienced

a WGD 8–18 Mya. Analyses of the common carp genome found a slow rate of gene loss, with 92% of the paralogs from the polyploid event still retained in both copies (88). In *Xenopus* frogs, there is significant pseudogene accumulation following an allopolyploidy event that occurred 17–18 Mya. Comparable to those in rainbow trout, around 64% of paralogs from the WGD experienced gene loss by pseudogenization (154). Different from the patterns observed in flowering plants, few large-scale gene deletions have been observed in animals. Most genes are deleted independently from neighboring genes by single-gene deletion (154). Notably, vertebrates represent all of the currently studied postpolyploid animal genomes. It is not clear if this pattern of gene deletion following WGDs is shared by all animals (14, 93).

The slow rate of gene removal in animals contrasts with the flowering plant–centric perspective that genes are rapidly deleted and genomes highly reorganized following WGDs. Slow gene deletion may impede the rate at which dosage balance problems are resolved following WGDs as well as reduce the rate of diploidization. The rapid gene deletion in flowering plants may allow them to resolve dosage balance problems much faster than animals. This hypothesis might help explain why polyploidy is rarer in animals compared to plants (102, 117, 125). Future studies should confirm if this pattern of gene deletion is shared by all animals. Recent genomic analyses revealed multiple paleopolyploidies in the ancestry of various invertebrate lineages, such as insects, horseshoe crabs, spiders, and mollusks (31, 62, 92, 122, 186). These ancient polyploids can be used to test if this pattern of gene deletion is shared by invertebrates. To test this hypothesis, one needs to assess the average rate of pseudogenization and gene deletion following polyploidy in animals and compare it to that in plants. Synteny analyses on high-quality animal and plant genomes are needed to estimate the average rate of gene loss. Variation in the rates and mechanisms of diploidization will likely be found. For example, a recent study using 13 *Paramecium* genomes shows a slower post-WGD gene loss rate compared to plants and vertebrates (61). Future studies are needed to further investigate the mechanisms and patterns of gene deletion following WGDs across eukaryotes.

Differences in the rate of diploidization between plants and animals may also impact diversification dynamics following polyploidy. A lag time between ancient WGD and diversification has been hypothesized to occur in plants (150). A recent study in salmonids suggests that potential lineage-specific ohnologue resolution (LORe)—which is mechanistically similar to the previously proposed divergent resolution hypothesis of Werth & Windham (174)—may result in delayed diploidization among lineages and could explain the lag time model in plants (24, 145). It is possible that the exceptionally slow rate of diploidization in salmonids may provide enough time for divergent resolution to occur in distinct lineages and contribute to diversification and adaptation. However, the evidence for divergent resolution is limited in plants. Previous studies have found that descendant lineages share similar genome organization with no evidence of significant differential and reciprocal genome evolution (44, 148). Further, Muir & Hahn (116) modeled the dynamics of divergent resolution and diversification following polyploidy. They found that divergent resolution required a stringent set of conditions to drive speciation, with population dynamics rather than genetics driving speciation dynamics (116). Better empirical estimates of diploidization rates are needed to model and assess if mechanisms such as divergent resolution can explain variation in speciation rates and genomic differentiation. This example highlights the need for understanding differences in the rate of diploidization between plants and animals.

FINAL THOUGHTS AND FUTURE DIRECTIONS

Diploidization involves a diversity of mechanisms to return polyploid genomes to an effectively diploid state. New comparative and population genomic data combined with cytogenetic and molecular biological approaches will continue to uncover the genetics and biology of the

mechanisms involved in diploidization. Perhaps the most important next step in improving our understanding of diploidization is developing a more rigorous and objective framework for testing hypotheses about diploidization. Many studies of diploidization are largely descriptive. This is fair because we are still in the relatively early days of discovering ancient WGDs and their legacies in eukaryotic genomes. As we move forward and more data become available, we need to work toward more explicit hypothesis testing of diploidization. There has been progress in this area for some aspects of diploidization, such as hypotheses on subgenome dominance (17). Developing model and simulation-based approaches to evaluate and test diploidization hypotheses would push the field forward. For example, model-based analyses of chromosomal evolution first introduced with chromEvol provided a new phylogenetic framework to test hypotheses of cytological evolution (108). Similar modeling and simulation approaches would permit researchers to more rigorously test hypotheses and develop more informed expectations about the outcomes of diploidization caused by different mechanisms and forces. Ultimately, the scale of data will demand more rigorous approaches as single-genome analyses make way for phylogenomic and population genomic investigations.

More rigorous analyses of diploidization will also allow us to address perhaps the most interesting question about the entire process: Why diploidize at all? Given the prevalence of diploidy among eukaryotes and the frequency of polyploid speciation in plants, we can deduce that polyploid species either diploidize or go extinct (4, 5). Why do polyploid species ultimately diploidize? It may be that bivalent pairing is inherently more stable than multivalent pairing and increases fitness. Perhaps bivalent pairing eventually leads to disomic inheritance and chromosomal differentiation by drift (85). Alternatively, diploidization may be driven to more efficiently purge deleterious substitutions in polyploid genomes (126). It may be that natural selection is more efficient in diploid genomes (113, 127), and selection in the environment, rather than the genome, drives diploidization. Model and simulation-based analyses of these and other hypotheses would provide new ways to explicitly test the ultimate causes and drivers of diploidization. Coupling comparative genomic analyses and data with studies that are explicitly aimed at measuring the fitness of the changes associated with diploidization are also needed. A challenge of studying diploidization is that many of the processes happen in that shadowy area of inference where the power of population genetics starts to fade but comparative phylogenetics may not be possible because of too few species. Moving forward, a combination of explicit models and simulations with data from carefully selected systems will help shine a light on the shadow of polyploidy.

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