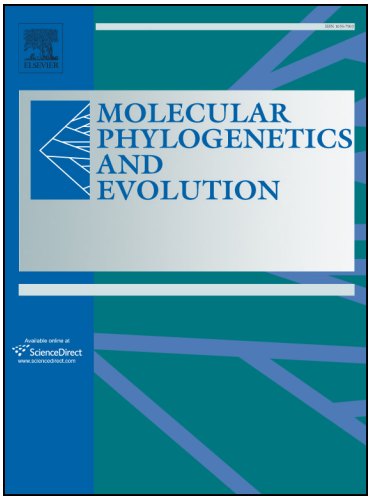

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PII: S1055-7903(16)30419-5
DOI: http://dx.doi.org/10.1016/j.ympev.2017.05.025
Reference: YMPEV 5838

To appear in: *Molecular Phylogenetics and Evolution*

Received Date: 9 December 2016
Revised Date: 25 May 2017
Accepted Date: 26 May 2017

Please cite this article as: Grusz, A.L., Sigel, E.M., Witherup, C., Homoeologous chromosome pairing across the eukaryote phylogeny, *Molecular Phylogenetics and Evolution* (2017), doi: http://dx.doi.org/10.1016/j.ympev.2017.05.025

Homoeologous chromosome pairing across the eukaryote phylogeny

Amanda L. Grusz[1, 5, 6], Erin M. Sigel[2, 5], Colby Witherup[3, 4]

[1]University of Minnesota Duluth, Department of Biology, 1035 Kirby Drive, Swenson Science Building 207, Duluth, MN 55803, USA; email: algrusz@d.umn.edu

[2]University of Louisiana at Lafayette, Department of Biology, 410 E. St. Mary Blvd, Billeaud Hall, Lafayette, LA 70503, USA

[3]Chicago Botanic Garden, Department of Plant Science, 1000 Lake Cook Road, Glencoe, IL 60022, USA

[4]Northwestern University, Program in Plant Biology and Conservation, Hogan Hall, Room 6-140B, 2205 Tech Drive, Evanston, IL 60208, USA

[5]Authors contributed equally.

[6]Corresponding author: algrusz@d.umn.edu (A.L. Grusz)

Abstract

During the past quarter century, molecular phylogenetic inferences have significantly resolved evolutionary relationships spanning the eukaryotic tree of life. With improved phylogenies in hand, the focus of systematics will continue to expand from estimating species relationships toward examining the evolution of specific, fundamental traits across the eukaryotic tree. Undoubtedly, this will expose knowledge gaps in the evolution of key traits, particularly with respect to non-model lineages. Here, we examine one such trait across eukaryotes—the regulation of homologous chromosome pairing during meiosis—as an illustrative example. Specifically, we present an overview of the breakdown of homologous chromosome pairing in model eukaryotes and provide a discussion of various meiotic aberrations that result in the failure of homolog recognition, with a particular focus on lineages with a history of hybridization and polyploidization, across major eukaryotic clades. We then explore what is known about these processes in natural and non-model eukaryotic taxa, thereby exposing disparities in our understanding of this key trait among non-model groups.

Abbreviations. ATP, adenosine triphosphate; DSBs, double strand breaks; MMR, mismatch repair; PCGs, pairing control genes; ROS, reactive oxygen species; WGD, whole genome duplication

Keywords. gene conversion, homoeolog, hybrid, meiosis, polyploid, recombination

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1. Introduction

Since the first issue of MPE was published 25 years ago, countless inferences of phylogenetic relationships have revolutionized our understanding of molecular evolution, particularly with respect to homology among shared traits. As we approach consensus among phylogenetic hypotheses for many groups, the use of evolutionary trees is acquiring new importance. Instead of simply asking how species have diverged over time, we can focus our attention on evolutionary patterns and processes as they relate to specific traits across the tree of life. Furthermore, with improved phylogenetic inferences in hand, we can better identify knowledge gaps in the evolution of key traits that span divergent lineages.

In this review, we examine homoeologous recombination as a case study, couched in a phylogenetic context, to illustrate that knowledge gaps spanning non-model systems limit inferences of broad evolutionary patterns across eukaryotes. Specifically, we review evidence for shared origins of the molecular machinery that guides homologous chromosome pairing during meiosis, and we provide a discussion of various meiotic aberrations that result in the breakdown of homolog recognition across major eukaryotic clades.

Defects in homologous chromosome recognition during meiosis can have severe evolutionary repercussions, such as offspring sterility, particularly in lineages characterized by polyploidy and/or hybridization between divergent parental genomes. But the breakdown of homolog recognition can also feasibly lead to beneficial genomic exchange (e.g., by generating novel allelic combinations via homoeologous exchange at a shared locus). In either case, the failure of chromosomes to recognize their homologous partners during meiosis, particularly in

polyploid hybrids, has potentially significant evolutionary implications for many eukaryotes (Comai, 2005). Substantial gaps remain in our understanding of both the underlying mechanisms responsible for meiotic chromosome pairing and the consequences of their failure among divergent lineages.

Diversification of eukaryotes is thought to have been inherently stabilized by the evolution of nearly ubiquitous sexual reproduction (Speijer et al., 2015), which is facilitated by the pairing of homologous chromosomes during meiosis. The emergence of sexual reproduction coincided with the incorporation of mitochondria, and thereby cellular respiration, into eukaryotic cells (McBride et al., 2006). Cellular metabolism brought with it endogenous production of ATP and the corresponding release of reactive oxygen species (ROS) as occasional byproducts of aerobic respiration (Hörandl and Hadacek, 2013); oxygen radicals destabilize DNA by removing electrons, creating a corresponding chain reaction of DNA damage. In meiosis, mechanisms that initially functioned in DNA repair have been co-opted to repair intentional double-strand breaks (DSBs) via the pairing and reciprocal exchange of sequences between homologous chromosomes (Hörandl and Hadacek, 2013). This reciprocal exchange between homologs is necessary for proper chromosomal segregation following metaphase of meiosis I and for the successful completion of meiotic cell division.

When homologous chromosomes fail to pair, meiosis goes awry. In some instances, the resulting meiotic products can have uneven or variously aneuploid chromosome complements. In others, particularly in organisms with a history of polyploidy or whole genome duplication, these errors can result in the pairing of related but evolutionarily divergent homologs, i.e., homoeologous chromosomes. Little is known regarding the extent of homoeologous chromosome pairing across eukaryotes, and the fundamental mechanisms guiding homolog

recognition have been described in only a few eukaryotic model systems (e.g., San Filippo et al., 2008).

In recent decades, we have gained an appreciation for the often pivotal role played by polyploidy in organismal—particularly eukaryotic—evolution (e.g., Dehal and Boore, 2005; Jiao et al., 2011; Glasauer and Neuhauss, 2014; Wolfe, 2015). Given the broad implications of whole genome duplication (Sémon and Wolfe, 2007; Conant et al., 2014), it is fitting to examine what is currently known about associated meiotic abnormalities, their causes, and their consequences across eukaryotes. Here, we review recent studies pertaining to homologous chromosome recognition, its breakdown, and the role of homoeologous chromosome pairing as it functions in naturally occurring eukaryotes, especially for those that have experienced contemporary or historical whole genome duplication. As expected, we find a dearth of information for broad swathes of the eukaryotic tree of life.

2. Review of meiotic chromosome recognition in eukaryotes

Proper segregation of homologous chromosomes in meiosis ensures the fertility of an organism and the genomic stability of its offspring while also promoting genetic diversity by generating novel combinations of parental alleles (Fisher, 1930; Muller, 1932). In a recent review, Zickler and Kleckner (2015) summarized how the pairing and subsequent segregation of homologous chromosomes is achieved by way of chromosomal recombination during meiosis I in organisms with canonical meiosis. Pairing is initiated by the formation of double-strand breaks: free ends of the DSBs invade corresponding regions of another chromosome, checking for sequence homology and forming a synaptonemal protein complex that binds the paired chromosomes. DSBs are then repaired by resolving the DNA heteroduplex as either the

reciprocal exchange (i.e., crossover or homologous recombination) or unidirectional exchange (i.e., non-crossover or gene conversion) of sequences between homologs. Associations between non-homologous chromosomes are arrested or repaired by partner switching, so that synapsis and genetic exchange occur exclusively between homologous chromosome pairs (Moore, 2002; Steward and Dawson, 2008). Chiasmata are formed at sites of crossover by late prophase I, thereby positioning the homologs for segregation at the beginning of anaphase I.

The efficacy of meiosis relies on chromosomes' ability to accurately and efficiently recognize and pair with their homologous partners among all other chromosomes in the nucleus. Based on studies of model systems (e.g., yeast, mouse, *Arabidopsis*) evidence suggests that the pairing of homologous chromosomes during meiosis is determined both prior and concomitant to meiotic recombination. These two stages and their associated mechanisms for homolog recognition are referred to, respectively, as recombination-independent and recombination-dependent chromosome pairing. However, observations of gene conversion and recombination among homoeologous chromosomes, as detailed in this review, suggest imperfections or inefficiencies can occur in homolog recognition, heteroduplex formation, and the dissolution of improper pairings. The genetic and structural mechanisms of meiotic chromosome recognition and pairing vary to some degree among plants, animals, and fungi. Below, we summarize genetic and structural mechanisms of meiotic chromosome recognition and pairing, and related anomalies leading to homoeologous exchange, highlighting variation in known mechanisms of homolog recognition among plants, animals, and fungi.

2.1. Recombination-independent mechanisms

Most eukaryotes depend on meiotic crossovers to regulate homologous chromosome recognition; however, studies increasingly show that many organisms utilize additional mechanisms prior to or in concert with synapsis to further facilitate homolog recognition and pairing (reviewed in Moore and Shaw, 2009; Ines et al., 2014). Recombination-independent mechanisms rely on physical placement and/or structural modifications to detect closely related homologs. For example, in some animals, yeast, and plants, chromosomes bind their telomeres to a concentrated region of the nuclear membrane during early leptotene of meiosis, forming a telomere bouquet (reviewed in Zickler and Kleckner, 2016). This process is mediated by the SUN and KASH nuclear envelope bridge proteins and meiosis-specific connector proteins, such as *Bqt1/2*, *ZIM*, and *Ndj1* (Hiraoka and Dernburg, 2009; Starr and Fridolfsson, 2010). Defects in SUN, KASH, and the various meiosis-specific connector proteins can lead to reduced recombination, indicating that although the telomere bouquet is not necessary for homolog recognition, it promotes efficient searching and pairing by bringing homologous chromosomes into close proximity (reviewed in Naranjo and Corredor, 2008; Koszul and Klecker, 2009). Such telomere association mechanisms vary, however, among model systems; for example, *Arabidopsis* telomeres cluster in the nucleolus rather than along the nuclear membrane (Armstrong et al., 2001). *Caenorhabditis elegans* and *Drosophila melanogaster* have specific pairing sites that bind to the nuclear membrane in lieu of a telomere bouquet (Tsai and McKee, 2011).

Structural or architectural features of chromosomes at early meiosis are also hypothesized to act as chromosome-specific identifiers, providing a rough, first pass at homolog recognition (Wilson et al., 2005). In male mice, for example, the meiosis-specific cohesin RAD21L is thought to facilitate homolog recognition by creating similar patterns of pericentromeric

heterochromatin clusters along homologous chromosomes; RAD21L mutants have decreased numbers of heterochromatin clusters and lack homolog association (Ishiguro et al., 2014; Ward et al., 2016). Similarly, mutations of the REC8 cohesin and associated Pds5 proteins reduce homologous pairing in the fission yeast *Schizosaccharomyces pombe* (Ding et al., 2016).

Chromatin changes associated with transcription may also facilitate homologous pairing. During transcription, actively transcribed regions are bound in factories of transcriptional proteins, such that chromosomes appear as linear arrays of factories and untranscribed heterochromatin; homologous chromosomes, with identical chromosome architecture, have identical or near-identical patterns of factories and heterochromatin (Cook, 1997). Homologous chromosomes are thought to be joined at the transcriptional factories or allelic transcription units, which then become target locations for recombination (Cook, 1997; McKee, 2004; Wilson et al., 2005; Ding et al., 2010). This is supported by observations that gene promoters are local hot spots for recombination in yeast, plants, and some mammals (Lichten and Goldman, 1995; Auton et al., 2013; Choi and Henderson, 2015; but see Baudat et al., 2013 for contrasting examples in mammals), and that strong pairing sites occur in highly transcribed ribosomal DNA (rDNA) loci and at histone genes in *Drosphila* (McKee, 2004). In a different but related mechanism, non-coding RNAs accumulate on their corresponding gene loci, potentially acting as targets for the passive agglutination of transcription factories on homologous chromosomes (Xu et al., 2006; Ding et al., 2012).

It seems likely that recombination-independent mechanisms of homolog recognition and pairing are error-prone because homology is determined by chromosome structure, a less stringent criterion than sequence similarity. In hybrid organisms, this allows for pairing between homoeologous chromosomes that have divergent sequences but retain similar gene synteny and

chromosomal architecture. Therefore, if subsequent mechanisms for homolog recognition at the nucleotide level fail (see section 2.2), hybrids formed from progenitors of low genetic divergence may still maintain bivalent, non-random chromosome pairing and some degree of fertility. For recombination-independent mechanisms, as divergence increases between progenitors, especially with respect to significant differences in chromosome structure, hybrids will likely experience decreased bivalent pairing and additional meiotic aberrations, particularly in the absence of contemporaneous genome duplication.

2.2. Recombinational mechanisms

The core genetic machinery regulating meiotic DSBs and homologous recombination is highly conserved, with homologs of the key proteins found in most eukaryotes (Ramesh et al., 2005; Mercier et al., 2015). An in-depth discussion of the molecular mechanisms controlling these processes is beyond the scope of this review, but several excellent papers have recently detailed the similarities and differences in DSB-associated proteins among organisms (e.g., Baudat et al. 2013; Lam and Keeney, 2015; Mercier et al., 2015; Zickler and Klecker, 2015). Among the many regulatory proteins, we briefly focus here on those that function in mismatch repair (MMR), for which there is substantial evidence that mutations and gene knock-outs yield increased incidence of non-homologous recombination and gene conversion.

All eukaryotes studied to date have homologs of MMR proteins (*Mut* proteins) that are hypothesized to play a significant role in identifying and preventing non-homologous base pairing during the initiation and resolution of the DNA heteroduplex, though their exact mechanisms are unknown (Spies and Fishel, 2015). Meiosis-associated MMR proteins are best characterized in interspecific yeast hybrids, in which deletion of the *Msh2* (*MutS* homolog) and

Pms1 (*MutL* homolog) genes increases homoeologous recombination up to 5-fold and reduces non-disjunction between homologous chromosomes, thus increasing hybrid viability (Hunter et al., 1996; Chambers et al., 1996). Such experiments suggest that meiosis-associated MMR proteins have anti-recombinational effects that impede the exchange of genetic material between evolutionarily divergent (i.e., homoeologous) chromosomes.

Subsequent studies indicate that the *Msh2* and *Pms1* loci display varying anti-recombinational effects based on the extent of chromosome divergence. In yeast for example, *Msh2* mutants and *Pms1* mutants both exhibited continuously decreasing rates of recombination in crosses between strains with up to 18% sequence divergence when compared to wild type yeast (Chen and Jinks-Robertson, 1999). In flowering plants, one study used inbred lines of *Arabidopsis* to demonstrate that deactivating the *AtMsh2* gene increased recombination 2- to 7-fold depending on percent divergence (0–9%) between homologous chromosomes (Li et al., 2006). Notably, recombination frequency decreased with increased sequence divergence in *Arabidopsis* progeny with fully functional *AtMSH2*, although to a lesser extent, further supporting the hypothesized existence of multiple, redundant mismatch or homolog recognition mechanisms (Borts et al., 2000).

Meiosis-associated MMR proteins provide a clear example of recombination-dependent homolog recognition, leveraging nucleotide base homology to prevent the illegitimate pairing of non-homologous chromosomes. As with other DSB repair-associated proteins, their various defects can be equally detrimental for the pairing of homologous chromosomes. However, MMR mutants may have potentially beneficial impacts as a result of homoeologous pairing between moderately divergent chromosomal homologs, such as the partial fertility of hybrid offspring.

2.3. Homolog recognition, pairing, and recombination in polyploids

In polyploid and hybrid organisms the complex processes of homolog recognition and pairing are further complicated by the presence of additional copies of homologous chromosomes and/or the presence of similar, but evolutionarily divergent, homoeologous chromosomes. As discussed above, the prevalence of homoeologous recombination in polyploid plant lineages is directly related to the level of evolutionary differentiation between the two parents. Parental genomes can range from being highly similar in autopolyploids to being more deeply divergent in allopolyploids. In allopolyploids with distantly related parents, chromosomes pair with their identical homolog and only bivalents are observed during metaphase I. Following normal chromatid separation in metaphase II, F1 individuals produce gametes with two complete sets of chromosomes from each parent. All subsequent generations exhibit strict bivalent chromosome pairing and homologous recombination.

In contrast, F1 progeny derived from parents of intermediate divergence frequently display a combination of bivalents and multivalents at metaphase I, due to the homoeologous pairing of some but not all parental chromosomes. In metaphase II, multivalents do not properly segregate, resulting in aneuploid gametes. In fertile individuals of subsequent generations (i.e., F2), a mix of bivalent and multivalent pairing occurs, with continued homoeologous recombination possible within multivalent associations, further increasing genetic diversity. These hybrids are referred to as segmental allopolyploids and include many major crop species (Stebbins, 1950). Meanwhile, in autopolyploids multivalent versus bivalent chromosome pairing appears to depend, respectively, on whether the polyploid is newly formed or belongs to an older, long-since stabilized lineage (see Bomblies et al., 2016).

Detailed examination of meiotic restitution pathways reveals an intimate link between chromosome pairing mechanisms and the prevalence of homoeologous recombination in polyploids. In fact, studies in numerous plant systems (e.g., wheat, oat, rye, cotton, coffee, tobacco; reviewed in Jenczewski and Alix, 2004; Naranjo and Benavente, 2015) have shown that pairing control genes (PCGs) enforce bivalent pairing between homologous chromosomes in some allopolyploids. By far, the best characterized PCG is the major dominant *Ph1* locus (Pairing homoeologous 1)—a cluster of defective *CdK*-related (cyclin-dependent kinase) genes—in allopolyploid wheat (*Triticum*; Cifuentes et al., 2009). These *CdK*-related genes have significant similarity to *Inducer of meiosis* (*IME2*) in budding yeast and *Cdk2* in mammals, which affect chromosome condensation via phosphorylation (Greer et al., 2012). *Cdk2* is required for proper homologous pairing and recombination in mammals (Viera et al., 2009). In wheat, *Ph1* appears to be a master coordinator of meiotic events, preferentially suppressing pairing and recombination between homoeologous chromosomes and correcting the formation of multivalents (Naranjo and Benavente, 2015).

While its exact mechanics are unknown, *Ph1* has been implicated in many recombination-independent events, such as the pairing of homologs at their centromeres before prophase (Martinez-Perez et al., 2001), the presynaptic alignment of chromosomes (Feldman, 1993), and changes in chromosome condensation that prevent DSBs from being repaired by homoeologous chromosomes (Greer et al., 2012). Indeed, the deletion of the *Ph1* locus allows homoeologous chromosomes to pair and recombine in wheat allopolyploids and interspecific hybrids (Riley, 1958; Sears, 1977), and induces major chromosome rearrangements and aneuploidy in progeny (Sanchez-Moran et al., 2001). *Ph1* likely has a regulatory role for genes that affect the fidelity of synapsis formation. For example, deletion of *Ph1* amplifies the activity

of *TaASY1* (*T. aestivum Asynapsis 1*)—a gene associated with proper formation of the synaptonemal complex—and increases multivalent formation at metaphase I (Boden et al., 2009). Additionally, the effects of *Ph1* on chromosome pairing are dosage dependent, with additional copies of *Ph1* further preventing homoeologous pairing. Beyond a given threshold, however, excessive copies of *Ph1* can actually result in a failure to correct synapsis between homoeologs. This suggests that an ideal dosage of *Ph1* (and closely associated loci) is needed to properly enforce homologous chromosome pairing (summarized in Moore, 2002). It is also increasingly clear that several minor loci enhance or suppress the actions of *Ph1*, such as *Ph2* which is thought to slow the progression of synapsis between homoeologous chromosome pairs (Martinez et al., 2001; Dong et al., 2002).

Other loci enforcing the bivalent pairing of homologous chromosomes have been identified in the allopolyploids *Brassica napus* and *Arabidopsis suecica,* although the genetic mechanisms underlying their effects are likewise unknown. The *PrBn* (Pairing regulator) in *B. napus* appears to have a major effect on the frequency of homoeologous crossovers with "high" and "low" frequency alleles inherited in a Mendelian fashion (Jenczewski et al., 2003). Like *Ph1*, the effects of *PrBn* could be dosage sensitive, with synthesized allotriploids of *B. napus* having increased rates of homoeologous pairing relative to allotetraploids (Nicolas et al., 2009). More recently, the *BYS* (BOY NAMED SUE) locus has been identified as a dominant locus contributing to homologous pairing during meiosis and, in turn, pollen viability, in the allotetraploid *Arabidopsis suecia* (Henry et al., 2014).

Our current knowledge of the genes involved in meiotic recombination and chromosome pairing is certainly incomplete. The identification and confirmation (through mutation or knockout experiments) of additional candidate homologous-pairing genes in model organisms is

essential for efficiently targeting these genes in non-model systems. Meiosis genes in general are poorly characterized in plants but relatively well characterized in yeast (Chen et al., 2010; Mercier et al., 2015). For example, in the flowering plant *Arabidopsis thaliana*, there are 62 genes in the TAIR database identified as being associated with recombination (Huala et al., 2001; The Arabidopsis Information Resource, 2016). Candidate chromosome pairing genes have also been identified in autopolyploid plants; selective sweeps in autotetraploid *Arabidopsis arenosa* revealed seven candidate meiosis genes for adaptive pairing, including ASY1, ASY3, PRD3, SMC3, SYN1, ZYP1a, and ZYP1b (Yant et al., 2013), all of which could serve as candidate genes for future research into allopolyploid homoeologous recombination.

2.4. The evolution of bivalent, homologous chromosome pairing

Little is known about the evolution of loci responsible for suppressing homoeologous pairing in animals and fungi. In plants, the independent, parallel evolution of pairing control mechanisms following hybridization and polyploidization is evident in multiple disparate lineages. For example, heightened signatures of divergent selection of *ASY1* (a homolog of *TaASY1*) in polyploids relative to diploids of *Arabidopsis* suggest that the same genetic pathways promote meiotic stabilization in wheat and *Arabidopsis* polyploids (Yant et al., 2013; Hollister, 2014). One hypothesis for the origin, and possible parallel nature, of pairing control mechanisms in allopolyploids is that alleles suppressing homoeologous recombination are preexisting at low frequencies in diploid progenitor populations, where they can have negligible or mildly beneficial effects (Waines, 1976). Upon allopolyploid formation, these preexisting pairing control alleles could impart an immediate benefit by enforcing homologous bivalent pairing and increasing fertility of the new allopolyploid. For example, particular genotypes of the diploid

ryegrass species *Lolium perenne* and *L. temulentum*, when crossed, produced allopolyploid progeny with reduced frequencies of multivalent associations and chiasma between homoeologous chromosomes (Taylor and Evans, 1977; Evans and Davies, 1985). Subsequent studies using isozyme and AFLP data present contradictory evidence that pairing control in *Lolium* allopolyploids is due to a single locus of large effect (e.g., *Ph1*) or many loci of small effect (Aung and Evans, 1987; Armstead et al., 1999).

Alternatively, mutations that suppress homoeologous pairing could have arisen at the time of allopolyploid formation, such as an antimorphic mutation (i.e., opposing normal gene function) in a pairing promoter or a hypermorphic mutation (i.e., increasing gene activity) in a preexisting pairing suppressor (Jenczewski and Alix, 2004). Such a mutation has been suggested for the origin of *Ph1*, as well as other PCGs in allopolyploid *Agropyron* (wheatgrass) and *Aegilops* (goatgrass; Dvorak, 1981; McGuire and Dvorak, 1982). In light of the high prevalence of meiotically-stabilized allopolyploids in plants (ca. 11% of plants; Barker et al., 2016), it is also possible that particular genes may be predisposed to mutation upon hybridization and whole genome duplication.

2.5. Additional factors influencing homoeologous pairing

In most organisms, the number and distribution of crossovers during meiosis are under stringent control (Mézard et al., 2007), but there is some evidence that both polyploidy and hybridization, in their own right, affect rates of meiotic recombination. For example, meiotic recombination in allopolyploids is significantly more frequent than in diploids of *Arabidopsis*, *Brassica*, and cotton (Brubaker et al., 1999; Leflon et al., 2010; Pecinka et al., 2011). Comparisons between artificially formed autopolyploids and diploids of the same genomic

composition in *Arabidopsis* suggest that whole genome duplication, when divorced from the effects of hybridization, leads to increased meiotic recombination (Pecinka et al., 2011). However, if alleles controlling improved pairing exist in natural populations at low frequencies (Waines, 1976), experiments that induce polyploidy in the lab may not trigger the same mechanisms used by natural polyploid populations.

Likewise, the age of a hybrid lineage may influence the prevalence of homoeologous pairing. Increased occurrences of meiotic aberrations in synthesized allopolypoids and allohaploids (e.g., in *B. napus* and *A. suecia*; Cifuentes et al., 2010; Grandont et al., 2014; Henry et al., 2014) suggest that younger hybrid lineages experience more homoeologous genetic exchange. Established autotetraploids of *A. arenosa* show a reduction in the number of crossovers (COs) per chromosome compared to the diploid ancestor and newly formed autotetraploids (Bomblies et al., 2016). The evolution of effective pairing mechanisms, while possibly accelerated in newly formed polyploids, may still require several generations to stabilize.

Environmental factors can greatly influence meiotic mechanisms and resulting crossover frequencies (reviewed in Bomblies et al., 2015). How changes in environment affect the frequency and success of homoeologous pairings has not, to our knowledge, been directly studied, but it is feasible that the environment could play a role. In normal meiosis, interlocking chromosomes—i.e., when a non-homologous chromosome becomes trapped inside a homologous chromosome pair—are resolved by a series of coordinated steps that include the proteins MLH1 and TOPOII (Bomblies et al., 2015; Modliszewski and Copenhaver, 2015). In both plants and animals, high temperatures can lead to the breakdown of interlock resolution. A suite of environmental factors, including high temperature, low temperature, drought, nutrient

availability, and chemical additives can lead to both increased and decreased crossover rates in plants and animals (Bomblies et al., 2015). Additionally, the production of unreduced gametes and rates of polyploid offspring increase in cold temperatures (De Storme and Mason, 2014), making polyploidy itself susceptible to environmental triggers.

Another factor that could, theoretically, promote homoeologous recombination is the polyploid ratchet effect (analyzed in Gaeta and Pires, 2010). This theory states that homoeologous recombination events create chromosomal regions of similarity on homoeologous chromosomes which are then recognized as homologous pairs in subsequent meiotic pairings; this results in more homoeologous recombination events creating additional regions of similarity for pairing recognition, and so on. Evidence for this phenomenon has been found in laboratory-synthesized polyploids at much higher rates than in natural populations, suggesting that genomic rearrangements of this sort may be selected against in natural populations (Gaeta and Pires, 2010).

3. Evidence for homoeologous chromosome pairing in eukaryotes

Here, we review naturally occurring examples of homoeologous recombination from across eukaryotes and review what is known regarding homolog recognition failure and homoeologous exchange in these taxa.

3.1. Homoeologous recombination in animals

Whole genome duplications have been documented in multiple animal lineages—most regularly in fishes and amphibians, as well as in other vertebrate and invertebrate groups (Mable

et al., 2011). Among these polyploid animals, evidence for homoeologous recombination during meiosis is currently restricted to fishes and amphibians.

3.1.1. Fishes

Within fishes, homoeologous exchange has been reported in both the cyprinid and salmonid clades, but at different evolutionary time scales. Recent homoeologous exchange has been inferred in a newly synthesized allotetraploid carp (*Cyprinus carpio* × *Carassius auratus*; Wang et al., 2015). By contrast, tetrasomic inheritance observed in the salmonid fishes and their close relatives (e.g., *Salmo*, *Salvelinus*, *Oncorhynchus*) is thought be driven by an ancient whole genome duplication that took place in their common ancestor (ca. 25–100 mya; Allendorf and Danzmann, 1997; Allendorf et al., 2015). Evidence of this ancient tetraploidy event is found in large, syntenic chromosome regions that are shared among distantly-related taxa, and in residual tetravalent chromosome pairing that takes place during male meiosis across the salmonid clade (Gharbi et al., 2006; Timusk et al., 2011).

Unlike with many non-model systems, the mechanisms of homoeologous pairing in salmonid fishes have been examined in detail. Early studies of rainbow trout (*Oncorhynchus mykiss*) led investigators to propose a two-step model explaining the tetrasomic inheritance that is observed at many loci in salmonid males (Allendorf and Danzmann, 1997). Allendorf and Danzmann (1997) hypothesized that homologous chromosomes initially pair and recombine in a region proximal to their centromeres, followed by secondary exchange when homoeologous chromosomes unite distally and recombine near their telomeres. Genomic evidence has since provided support for this hypothesis (e.g., Lien et al., 2011; Allendorf et al., 2015). These authors also presented a two-tiered model for the evolution of disomic inheritance in which the gradual evolution of disomy takes place through nucleotide divergence and that rapid shifts

toward disomic inheritance more likely result from chromosome structural rearrangements. Additional evidence from the genus *Salmo* indicates that, along with the shared retention of homoeologous tetravalent associations among salmonid fishes, the locations of homoeologous pairing are similarly consistent among divergent species (Brieuc et al., 2014). This suggests high fidelity in chromosome evolution among the descendants of an ancient, polyploid, salmonid ancestor.

3.1.2. Amphibians

Beyond fishes, the best documented examples of homoeologous recombination in animals are from allopolyploid salamanders belonging to the *Ambystoma jeffersonianum* complex, in which reticulate evolution among bisexual species has contributed to more than 20 parthenogenetic hybrids (Bi and Bogart, 2006). Genomic in situ hybridization (GISH) studies of two allotriploid hybrids revealed clear bivalent pairing among chromosomes at metaphase, as well as homoeologous recombination (Bi and Bogart, 2006). Specifically, genetic exchange was observed in a pair of subtelocentric chromosomes, in a distal region of each long arm, and in a pair of large, homoeologous metacentric chromosomes spanning sizable exchange blocks (Bi and Bogart, 2006). The mechanisms allowing for homoeologous pairing in *Ambystoma* hybrids are unknown, but further studies, particularly those focused on premeiotic genome duplication, will surely expand our understanding of meiosis in these parthenogenetic polyploid amphibians.

3.2. Homoeologous recombination in plants

Among eukaryotes, homoeologous recombination is best understood in plants, probably owing to a high incidence of polyploidy and hybridization in many domesticated crops (Hancock, 2012). Extensive cytological studies in these groups have improved our grasp of

meiotic chromosome pairing and its aberrations in agriculturally important species of wheat, rice, cotton, and mustards. However, intergenomic exchange is not restricted to these well-studied groups; it has also been documented in related, non-model and/or lesser-known taxa. In the following sections, we briefly survey studies for which homoeologous chromosome pairing has been reported in plants.

3.2.1. Crops and related model systems

Genomic exchange between divergent crop species is of special interest as a tool for the introgression of novel traits in agricultural breeding programs (Qi et al., 2007). For this reason, homoeologous recombination has been particularly well studied in many polyploid crops, including cereals (i.e. grasses; order Poales), mustards (order Brassicales), and cotton (order Malvales). Interestingly, early investigations in the cereal wheat (*Triticum*) exposed a notable absence of homoeologous recombination in allopolyploid taxa (Sears, 1976). Studies in both cereals and mustards have since revealed that novel genetic systems, thought to have evolved possibly following polyploidization, function to mitigate non-homologous chromosome pairing during meiosis in these groups (e.g., *Ph1* and *PrBn* loci; see section 2.2). Given the stability imparted by these regulatory loci, it is conceivable that similar systems might function in other plant lineages, but most remain unexplored.

Grasses—The ancestor of modern grasses underwent a whole genome duplication ca. 50–70 mya, the descendants of which exhibit significant variation in genome size and structure (Bennetzen, 2007). Despite this, gene content is surprisingly well conserved across the family and gene synteny appears to be largely retained among extant taxa (Bennetzen, 2007). High colinearity in regions of increased recombination in wheat and rice (as well as in mustards;

Bowers et al., 2005) could be guided in part by genetically regulated homologous chromosome pairing (e.g., by *Ph1* or *PrBn*). However, while most protein coding genes in *Triticum* show a high degree of homoeolog retention, there is also evidence for homoeologous gene conversion in this group, especially within large syntenic regions (Feldman et al., 2012). Similarly, comparisons among species of rice (*Oryza*) indicate relatively recent (< 4 mya) long-range gene conversion near chromosome termini (Jacquemin et al., 2011). In these examples, gene conversion may facilitate redundancy in telomeric and subtelomeric chromosome regions, thereby obscuring distinctions between homologs and homoeologs (Jacquemin et al., 2011).

In grasses, evidence of homoeologous exchange has been well documented in several allopolyploid taxa using a variety of experimental approaches. Examples include hybrids between *Lolium* and *Festuca* (Zwierzykowski et al., 1999, 2008) and between *Triticum* and *Hordeum* (Bildanova et al., 2003). Evidence from AFLPs in *Spartina* allopolyploids also indicates the possibility of gene conversion in some species, but further study is needed (Ainouche et al., 2004; Salmon et al., 2005). Additionally, in allohexaploid oats (*Avena sativa*)—which appear to lack a *Ph1*-like homolog recognition system—multivalents and unidirectional homoeologous translocations among parental chromosomes are frequent during meiosis I (Nikoloudakis and Katsiotis, 2015).

Other monocots—Outside of the grasses, evidence for homoeologous chromosome pairing has been documented in other monocot lineages with horticultural and/or agricultural utility, including members of the orders Asparagales, Liliales, and Zingiberales. In most cases, chromosome painting has been employed to expose homoeologous recombination in interspecific and intergeneric hybrids (e.g., *Allium*: Stevenson et al., 1998; *Alstroemeria*: Ramanna et al., 2003; *Aloe* × *Gasteria*: Takahashi et al., 1997). Using AFLP and simple

sequence repeat (SSR) markers, homoeologous exchange has also been documented in polyploid bananas (*Musa*; Crouch et al., 1999). In *Musa*, high levels of homoeologous recombination in tetraploid hybrids, speculated to result from low levels of genetic differentiation between the parental genomes, have been utilized as a tool for the introgression of novel traits into this popular food crop (Crouch et al., 1999).

Rosids—Within angiosperms, homoeologous recombination is especially well studied within the rosid clade, particularly in the mustards (which include *Arabidopsis*; order Brassicales) and in cotton (*Gossypium*; order Malvales).

In mustards, early work united cytology, isozyme analyses, and selective breeding to explore genome interactions in hybrids. For example, Eber and colleagues (1994) examined hybrids between male-sterile *Brassica napus* (a tetraploid hybrid between *Brassica rapa* and *B. oleracea*) and two related, weedy relatives, *B. adpressa* and *Raphanus raphanistrum*. Their study recovered no evidence of homoeologous pairing between parental genomes in the *B. napus* × *adpressa* hybrids, but intergeneric *Brassica* × *Raphanus* hybrids exhibited prevalent multivalent associations, leading the authors to speculate on the potential for homoeologous recombination (Eber et al., 1994). Studies of allotetraploid *B. napus*, however, did not reveal significant homogenization between its *B. rapa* and *B. oleracea* parental genomes except for the putative preferential incorporation of transposable elements derived from *B. oleracea* (Howell et al., 2008).

Subsequent studies have expanded our knowledge of homologous and homoeologous interactions within the allotetraploid *B. napus* (Gaeta and Pires, 2010), especially regarding dosage-dependent effects of the homologous pairing locus *PrBn* (Jenczewski et al., 2003; Nicolas et al., 2009; Cifuentes et al., 2010; Cui et al., 2012). It is now clear that the chromosome

pairing behavior of newly synthesized *B. napus* hybrids differs dramatically from that of naturally formed *B. napus* allotetraploids; the former exhibit large-scale genome restructuring, including homoeologous recombination in the F1 generation, whereas the latter show relative genome stasis, with only rare homoeologous exchanges (Gaeta and Pires, 2010; Nicolas et al., 2009; Szadowski et al., 2011; Cui et al., 2012). When homoeologous recombination does occur, it most frequently takes place between homoeologous chromosome pairs with expansive colinear regions, but this depends in large part upon the presence or absence of closely-related homologs (Nicolas et al., 2008 and citations therein). The natural allotetraploid bittercress, *Cardamine flexuosa* (order Brassicales), conveys near-complete genome stability and homologous pairing. Only a single homoeologous reciprocal translocation has been detected in *C. flexuosa* (Mandáková et al., 2014), supporting the idea that a *PrBn*-like homologous pairing regulator may also be functioning in this *Brassica* relative.

Much like in *Brassica*, genome interactions within domesticated cotton (e.g., *Gossypium hirsutum* and *G. barbadense*) have been the subject of extensive study (Wendel, 2000). Various systematic approaches have been used to show that *G. hirsutum* and *G. barbadense*, together with three wild relatives, are the result of an ancient hybridization event estimated to have taken place ca. 1.5 mya, and thus each comprises the same two divergent parental genomes (i.e., the A-genome and D-genome; Wendel and Cronn, 2003). Early analyses based on ribosomal ITS sequences, however, showed that homoeologous exchange among parental genomes in these allopolyploids has led to bi-directional, concerted evolution of rDNA, such that four of the five species possess only the D-genome at this locus, while the fifth has only the A-genome (Wendel et al., 1995).

Several studies have since reinforced these findings, further demonstrating that gene conversion is the primary driver of homoeologous exchange in *G. hirsutum* (Salmon et al., 2010; Flagel et al., 2012; Page et al., 2013). As observed in allopolyploid wheat, such non-reciprocal homoeologous recombination events span regions of only a few base pairs up to nearly a megabase in length (Salmon et al., 2010). Recent work has also exposed the surprising extent of homoeologous gene conversion in *Gossypium*, which is evident in 1.8–5% of contigs examined (Salmon et al., 2010; Flagel et al., 2012). More than 1,400 loci in *G. hirsutum*, roughly 25% of which are shared with *G. barbadense*, show further signatures of gene conversion (Page et al., 2013) indicating that some homoeologous exchanges occurred soon after the ancestral polyploidization event predating the divergence of *G. hirsutum* and *G. barbardense*, whereas other exchanges have occurred more recently, following the evolution of these two species (Flagel et al., 2012).

The documentation of widespread homoeologous gene conversion in domesticated cotton is complemented by observations of bivalent chromosome pairing and an absence of reciprocal homoeologous exchange (Salmon et al., 2010). This lack of recombination may result from size disparities between homoeologous chromosomes resulting from the insertion of transposable elements into the A-genome (Grover et al., 2007). Alternatively, while genetic regulation of homologous pairing in meiosis has not been described in allopolyploid cotton, high fidelity in bivalent pairing could indicate the presence of pairing control genes. The resolution of non-crossovers prior to chiasmatic associations (Allers and Lichten, 2001) would, in turn, explain gene conversion in this group.

Homoeologous exchange has been infrequently documented in rosid lineages outside of mustards and cotton. Evidence for tetrasomic inheritance in the cultivated allotetraploid peanut

was gathered from gene expression and genotyping data (*Arachis*; Leal-Bertioli et al., 2015), and in allotetraploid sour cherry, *Prunus cerasus*, Wang et al. (1998) uncovered AFLP banding patterns that were consistent with intergenomic pairing and/or recombination. Unfortunately, in the case of *P. cerasus*, the limitations of dominant AFLP markers prevented the authors from confirming this hypothesis with certainty.

Asterids—The asterid clade is home to several well-known crops, such as tomatoes, potatoes, and tobacco, that serve as systems for studying genome dynamics within allopolyploids. *Nicotiana* in particular (which includes tobacco, *N. tabacum*), encompasses more than 35 allotetraploids, including several well-studied hybrids ranging from newly synthesized taxa to long-established, stable polyploid species (Clarkson et al., 2010). Studies show that the number of copies and location of rDNA in the natural polyploid hybrids (e.g., *N. rusticum*, *N. arentsii*, and *N. tabacum*) are largely additive of their respective progenitor taxa, but in some cases rDNA may be partially or completely homogenized by gene conversion to favor copies from one progenitor (Kovarik et al., 2004; Lim et al., 2004). When compared to artificially synthesized lineages, the wild allotetraploid *N. tabacum* exhibits relative genome stability and a lack of homogenization among rDNA loci (Kovarik et al., 2004). Likewise, the natural allotetraploid *N. arentsii* lacks intergenomic homogenization at subtelomeric loci (Matyasek et al., 2011). It has been hypothesized that the degree of sequence and structural divergence in critical telomeric and/or centromeric regions influences the extent of genome homogenization (or lack thereof) in these allopolyploid taxa (Matyasek et al., 2011).

Early chromosome work by Menzel (1964) in tomatoes and their wild relatives provided a preliminary glimpse into chromosome homology and pairing in the group. Specifically, Menzel examined meiotic chromosome pairing regimes in newly-synthesized *Lycopersicon esculentum*

× *Solanum lycopersicoides* F1 diploid hybrids and in the corresponding colchine-induced allotetraploid. F1 hybrids demonstrated synapsis among homoeologs during meiosis, despite evidence for preferential homologous chromosome pairing in the allotetraploid (Menzel, 1964). Further investigations of *S. lycopersicoides* introgression lines in a *L. esculentum* genetic background showed additional evidence for homoeologous pairing and exchange, with increased recombination rates in regions of shared homology (Canady et al., 2006). Within *Lycopersicon*, chromosome painting of newly synthesized allohexaploids (*L. esculentum* × *L. peruvianum*) revealed a high incidence of homoeologous recombination, with chiasmata frequently detected in subterminal chromosome segments (Parokonny et al., 1997).

While newly synthesized allopolyploids from across the Solanales show increased genome rearrangement and restructuring, studies in members of the Lamiales show otherwise. In particular, analysis of several microsatellite loci suggests that the synthetic neoallotetraploid *Mimulus sookensis* exhibits strict homologous pairing during meiosis, although phenotypic variation in corresponding downstream offspring indicate the possibility of rare recombination events (Modliszewski and Willis, 2014).

Outside of cultivated crops, *Tragopogon mirus* and *T. miscellus* (Asterales) are, by far, the best-studied natural cases of allopolyploidy in the asterid clade. These now-classic examples of recently formed allotetraploids were derived through hybridization of *T. dubius* with *T. porrifolius* and *T. pratensis*, respectively, upon their introduction into the western United States in the early 1900s (Owenby, 1950; Soltis et al., 2004). Comparisons of synthetic and naturally formed individuals of *T. miscellus* and *T. mirus* suggest that the frequency and direction of homoeologous exchange in these allotetraploids depends upon the age and origin of each lineage. For example, rDNA studies of herbarium specimens (collected in 1949) showed that in early

populations of both allotetraploids parental rDNA loci appeared to be inherited in equal proportions. However, in more recent, wild-collected material of both *T. mirus* and *T. miscellus*, rDNA from the *T. dubius* parent was significantly decreased, possibly owing to unidirectional gene conversion (Soltis et al., 2004; Kovarik et al., 2005); however, inferences from other repetitive sequence data revealed no major genomic rearrangements in recently collected populations of either species (Soltis et al., 2004; Pires et al., 2004). By contrast, artificially synthesized individuals of *T. miscellus* and *T. mirus* exhibited frequent multivalent formation and regular intergenomic translocations (Lim et al., 2008).

3.2.2. Bryophytes and ferns

Outside of agriculturally important angiosperms and their relatives, little has been done to explore homoeologous pairing and exchange in other plant lineages, with the exception of ferns. To our knowledge, the only study examining homoeologous exchange in non-vascular plants is in the bryophyte model system, *Physcomitrella patens* (Trouiller et al., 2006). Research by Trouiller and colleagues (2006) tested the influence of MSH2 (a major MMR locus) on homoeologous pairing in *P. patens*, but their work was limited to in-vivo gene targeting experiments using synthetic DNA (Trouiller et al., 2006). Even so, the authors found that MSH2 knockouts allowed for increased homoeologous pairing in sequences with up to 3% genetic divergence, compared to samples with wild type MSH2 (Trouiller et al., 2006).

Ferns, by contrast, are among the first vascular, non-model lineages in which homoeologous chromosome pairing was examined in detail. For example, Klekowski and Hickok (1974) examined the inheritance of a phenotypic marker among synthetic inbred lines of the allotetraploid fern *Ceratopteris thalictroides* and found patterns consistent with

homoeologous pairing and recombination. Later, Hickok (1978) contributed additional observations of segregation for the same phenotypic marker in F3–F5 generations and estimated the rate of homoeologous recombination to be 10%. Studies of inbred lines derived from wild-collected individuals of *Pteridium aquilinum*, using polymorphic enzyme banding patterns, also showed clear patterns of non-sister pairing and segregation, but in this case among duplicated homologous chromosomes resulting from autopolyploidy (Chapman et al., 1979).

Interestingly, in many apomictic ferns chromosome interactions are further complicated by premeiotic genome duplication accompanying sporogenesis (Döpp, 1932; Manton, 1950; Grusz, 2016). This temporary whole genome duplication results from restitutional mitosis immediately preceding meiosis (i.e., premeiotic endomitosis); meiosis I commences with double the (oftentimes already polyploid) parental genome complement (Döpp, 1932; Manton, 1950; Grusz, 2016) and the corresponding cells exhibit strict bivalent pairing among chromosomes (Bierhorst, 1975). This process of diploid meiocyte production is not unique to ferns and has also been documented in several vertebrate lineages (Stenburg and Saura, 2009), including the *Ambystoma jeffersonianum* complex, which, as mentioned above, exhibits homoeologous exchange (see section 3.1; Bi and Bogart, 2006).

Homoeologous recombination in an apomictic allopolyploid was first documented in the wild-collected allotetraploid species *Trichomanes pinnatum* (Bierhorst, 1975) through the movement of a paracentric inversion among related inbred lines. Homoeologous and/or non-sister chromosomal exchange has since been detected in several additional apomictic polyploid ferns by tracking the inheritance of singular enzyme/DNA markers in *Cyrtomium* (Ishikawa et al., 2003) and *Dryopteris* (Ootsuki et al., 2012), or multiple microsatellite loci in *Myriopteris* (Grusz, 2016).

3.3. Homoeologous recombination in fungi

Studies of polyploidy and hybridization in fungi have revealed striking parallels with allopolyploidy in plants. Multiple fungal clades exhibit contemporary whole genome duplication (e.g., the phyla Basidiomycota, Blastocladiomycota, Glomeromycota, and Mucoromycotina) and reticulate evolution has been observed in members of both the basidiomycete and ascomycete lineages (Albertin and Marullo, 2012). Even so, detailed investigations have almost exclusively targeted members of the genus *Saccharomyces* (Ascomycota).

The best example of homoeologous recombination within *Saccharomyces* comes from the lager yeast, *S. pastorianus*, which exhibits large chromosomal and structural rearrangements between its corresponding parental subgenomes, *S. cerevisiae* and *S. bayanus* (or an *S. bayanus*-like relative; Albertin et al., 2009; Albertin and Marullo, 2012). Conserved hot spots of recombination have been observed among domesticated strains of *S. pastorianus* (Usher and Bond, 2009), along with the preferential retention of alleles from the *S. bayanus* parent in some cases (Muller and McCusker, 2009). While much remains to be learned about the molecular dynamics of recombination in hybrid lager yeasts, a possible correlation exists between translocation breakpoints and certain genomic elements in some strains (e.g., tRNA, TE, or replication origins; Dunn and Sherlock, 2008).

Beyond *Saccharomyces*, meiotic homoeologous recombination has also been loosely explored in members of the Ascomycota, Basidiomycota, and Blastocladiomycota. For example, quadrivalents or secondary associations of homoeologous chromsomes during diplotene and diakinesis have been observed in the allotetraploid fungus *Cyathus stercoreus* (Basidiomycota;

Lu, 1964) and concerted loss of rDNA has been detected in the allopolyploid ascomycete *Botrytis aclada* (Nielsen and Yohalem, 2001).

Early studies of hybridization, polyploidy, and chromosome evolution in the aquatic genus *Allomyces* (Blastocladiomycota) leveraged morphological and cytological characters to expose allotetraploid hybrids derived from parental species with different chromosome numbers (Emerson & Wilson, 1954). However, while F1 hybrids frequently exhibited a combination of bivalents and univalents during meiosis, bivalent formation was inferred to result from the putative pairing of identical homologues (Emerson & Wilson, 1954).

4. Concluding remarkss

As illustrated in this review, various molecular mechanisms are known to regulate homologous chromosome pairing in polyploid lineages across the eukaryotic tree of life. Consequentially, many lineages exhibit strict fidelity in bivalent homologous exchange, while some show evidence of extensive reciprocal homoeologous recombination, and still others display only unidirectional gene conversion in specific chromosomal regions (e.g., at the telomeres) or at particular loci (e.g., rDNA). The mechanisms guiding these patterns of exchange may be convergent, e.g., in the possible case of homologous pairing control genes *PrBn* and *Ph1*. In other situations, pairing control mechanisms may be altogether absent, or may develop well after the origin of a given allopolyploid lineage. Regardless of the underlying mechanisms involved, it is clear that a broad phylogenetic perspective reveals similarities and disparities in the functionality of homologue recognition among divergent taxa, providing a more holistic view of the evolution of this particular set of traits. It is also evident that large gaps remain in our understanding of this trait for large sections of the eukaryotic tree of life.

Next generation molecular tools are now accessible for all branches of the tree of life; with these in play, we can more effectively probe the origins and evolution of myriad traits shared among deeply divergent eukaryote lineages. As we move toward a comprehensive understanding of evolutionary relationships among organisms, it will become increasingly feasible to examine a variety of fundamental traits not just among closely related taxa, but spanning the eukaryote phylogeny and beyond. As more non-model systems continue to be explored, evolutionary generalities based on examples from model systems alone are sure to become thing of the past. Inevitably, more extensive examinations will reveal significant holes in our understanding of key traits for most eukaryotic taxa, thereby indicating that an increased focus on non-model taxa will surely provide the foundation for the next paradigm in evolutionary phylogenetic studies.

Acknowledgements. The authors thank editors and reviewers for their constructive feedback regarding this contribution. In particular, we extend appreciation to the many mentors and colleagues at our various institutions for stimulating discussions and kindly reviewing early versions of the manuscript.

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Glossary

Allopolyploidy: Having three or more chromosome sets inherited from multiple parental species.

Apomictic: Reproducing through spore or seed without the fusion of gametes, usually associated with failure to reduce chromosome number during meiosis ($n = 2n$).

Aneuploidy: An organism whose chromosome number differs from wild type by part of a chromosome set (Griffith et al., 2000); i.e., $2n + 1$ (trisomic) or $2n - 2$ (nullisomic).

Autopolyploidy: Having three or more chromosome sets inherited from a single parental species.

Bivalent: The pairing of two, typically homologous, chromosomes physically united by one or more chiasma at metaphase I of meiosis.

Chiasma (plural *Chiasmata*): Point of contact between paired chromosomes during metaphase I of meiosis; location at which crossing over, or recombination, has occurred between chromosomes.

Crossover: See *Meiotic Recombination*.

Homology: Similarity in DNA sequence and/or gene order; referring to pairs of chromosomes or chromosome sets derived from the same parental species.

Homoeology: Similarity in DNA sequences or structure that share ancestral homology but have experienced significant evolutionary divergence; referring to chromosomes or chromosome sets derived from different parental species.

Homoeologous exchange: A general term referring to either meiotic recombination (i.e., crossover) or meiotic gene conversion (i.e., noncrossover) between homoeologous chromosomes.

Meiotic Recombination: Bidirectional exchange of genetic material resulting from the pairing of chromosomes; results in the production of gametes with different allelic complements than the parent.

Meiotic Gene Conversion: Unidirectional exchange of genetic material between paired chromosomes during prophase I.

Multivalent: The pairing of three, typically homologous and/or homoeolgous, chromosomes physically united by chiasmata at metaphase I of meiosis.

Noncrossover: See *Meiotic Gene Conversion*.

Parthenogenetic: A form of asexual reproduction in which the zygote develops from an unfertilized egg.

Synaptonemal Complex: A zipper-like protein structure that forms between aligned chromosomes during prophase I, which facilitates pairing recombination.

Figure legend.

Figure 1. Phylogenetic distribution of meiotic homoeologous chromosome pairing as documented across eukaryotes. Major eukaryotic lineages with evidence for homoeologous exchange in black. Genera with direct evidence for homoeologous pairing and/or exchange in dark orange; genera with indirect evidence for homoeologous pairing and/or exchange in pale orange.

Highlights

- Studies in model systems have illuminated the primary mechanisms of meiotic chromosome pairing in eukaryotes.
- Multiple redundant measures prevent homoeologous chromosome exchange in model groups.
- Failure at various stages of homolog recognition can lead to homoeologous recombination and gene conversion.
- Major gaps remain in the study of meiotic chromosome exchange across non-model eukaryotes.