Review

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Patterns, mechanisms, and consequences of homoeologous exchange in allopolyploid angiosperms: a genomic and epigenomic perspective

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Summary

Allopolyploids result from hybridization between different evolutionary lineages coupled with genome doubling. Homoeologous chromosomes (chromosomes with common shared ancestry) may undergo recombination immediately after allopolyploid formation and continue over successive generations. The outcome of this meiotic pairing behavior is dynamic and complex. Homoeologous exchanges (HEs) may lead to the formation of unbalanced gametes, reduced fertility, and selective disadvantage. By contrast, HEs could act as sources of novel evolutionary substrates, shifting the relative dosage of parental gene copies, generating novel phenotypic diversity, and helping the establishment of neo-allopolyploids. However, HE patterns vary among lineages, across generations, and even within individual genomes and chromosomes. The causes and consequences of this variation are not fully understood, though interest in this evolutionary phenomenon has increased in the last decade. Recent technological advances show promise in uncovering the mechanistic basis of HEs. Here, we describe recent observations of the common patterns among allopolyploid angiosperm lineages, underlying genomic and epigenomic features, and consequences of HEs. We identify critical research gaps and discuss future directions with far-reaching implications in understanding allopolyploid evolution and applying them to the development of important phenotypic traits of polyploid crops.

I. Introduction

Polyploidy through whole genome duplication (WGD; Box 1) is a recurrent, ubiquitous feature in the history of eukaryotes and is often linked with the origin of key innovations found in major eukaryotic lineages (e.g. flowers in angiosperms; McLysaght et al., 2002; Otto, 2007; Schranz et al., 2012; Edger et al., 2015; Soltis & Soltis, 2016; Van de Peer et al., 2017). Whole genome duplication is particularly common and widespread across flowering plants, with over 180 putative events identified in the angiosperm phylogeny (Leebens-Mack et al., 2019). Evidence suggests that all extant flowering plants are descendants of a polyploid common ancestor, and this duplication provided the evolutionary substrate for the development of the flower leading to the ecological success of flowering plants (Jiao et al., 2011; Leebens-Mack et al., 2019).

A multitude of lineage-specific polyploid events has spurred the evolution of flowering plants leading to a recurring cycle of polyploidization and then return to a diploid-like state (Soltis et al., 2009; Jiao et al., 2011; Wendel, 2015; Soltis & Soltis, 2016; Mandakova & Lysak, 2018; Leebens-Mack et al., 2019). Polyploid species show evidence of extensive chromosomal rearrangements, genome fractionation, epigenetic modifications, and diversification – commonly known as postpolyploidy genomic responses (Wendel, 2015; Soltis et al., 2016; Wendel et al., 2018). These, among many short- and long-term postpolyploidy changes, lead to cytological diploidization – the restoration of diploid-like chromosome pairing behavior during meiosis – and genic diploidization – the loss of duplicated genes – collectively referred to as diploidization (Conant et al., 2014; Mandakova & Lysak, 2018). The fate of duplicated genomes is determined through the eventual resolution of cytological diploidization. The extent of genic diploidization will vary based on factors including timing of subsequent polyploid events, divergence between the parental genomes in a polyploid, and lineage-specific variation of genome function (Geiser et al., 2016; Li et al., 2016; Mandakova et al., 2017; Z. Li et al., 2021). Despite progress to describe postpolyploidy evolutionary processes, our understanding of mechanisms that enable polyploid genomes to return to a diploid-like state and drivers of variation in the diploidization process across species and WGD events is still in its infancy (Z. Li et al., 2021).

Polyploids are grouped into two broad categories representing opposite ends of a continuum of similarity: autopolyploids and allopolyploids (Stebbins Jr., 1947; Ramsey & Schemske, 1998). Autopolyploids result from genome doubling within a species or genetically similar individuals (Doyle & Egan, 2010) and exhibit unique biological challenges, such as a prevalence of multivalent chromosome pairing due to the high similarity of the genome copies (Ramsey & Schemske, 1998; Mason & Wendel, 2020; Z. Li et al., 2021). Allopolyploidy results in organisms containing genomes from two or more progenitor species, referred to as subgenomes, each with a distinct evolutionary history, and these allopolyploids predominantly exhibit bivalent chromosome pairing (Fig. 1a,b; Ramsey & Schemske, 1998; Mason & Pires, 2015; Edger et al., 2018; Mason & Wendel, 2020; Z. Li et al., 2021). Between the two ends of the spectrum, other polyploid species present a mosaic-like genome of auto- and allopolyploid sections where some regions of the subgenomes are identical while others are distinct, displaying a mix of both bivalent and multivalent chromosome pairing – known as segmental allopolyploidy (Stebbins Jr., 1947; Mason & Wendel, 2020; Z. Li et al., 2021). A recent survey on 118 extant allopolyploids showed that 51.7% experienced at least some form of multivalent pairing, suggesting segmental allopolyploidy is potentially pervasive among polyploid plant species (Z. Li et al., 2021). Having ancestrally similar but not identical chromosome sets – also known as homoeologous chromosomes – leads to several unique challenges during diploidization for allopolyploids compared with autopolyploids as they reconcile separate genomes into a single functioning nucleus (Fig. 1a–g; Comai, 2005; Bomblies et al., 2016; Bomblies, 2020, 2022; Gonzalo, 2022).

The joining together of evolutionarily distinct subgenomes and subsequent evolution can lead to novel phenotypes, patterns of gene expression, transposon content, regulatory elements, chromatin conformation, and changes in genome structure (Osborn et al., 2003a; Birchler & Veitia, 2012, 2014; Conant et al., 2014; Bird et al., 2018; Blischak et al., 2018; Doyle & Coate, 2019; Baniaga et al., 2020; Soares et al., 2021; Van de peer et al., 2021; Blasio et al., 2022). Besides these genetic and epigenetic responses, one unique challenge in the early generations of allopolyploids is retaining chromosome pairing between homologs and suppressing homoeologous pairing during meiosis (Gaeta & Pires, 2010; Henry et al., 2014; Mason & Pires, 2015; Lloyd & Bomblies, 2016; Pele et al., 2018; Glombik et al., 2020; Martın et al., 2021; Nyarko & Mason, 2021; Soares et al., 2021; Wang et al., 2021). The maintenance of proper homologous pairing and suppression of the pairing and recombination between homoeologous chromosomes can be driven by a high degree of divergence between homoeologs and/or the presence of meiotic control loci (Riley & Chapman, 1958; Jenczewski et al., 2003; Zhang et al., 2020). Nonetheless, homoeologous chromosome pairing and recombination frequently occur and are tolerated, as observed in numerous allopolyploids (Chester et al., 2012; Chalhoub et al., 2014; Lashermes et al., 2014, 2016; Z. He et al., 2017; Higgins et al., 2018, 2021). When homoeologous recombination (i.e. homoeologous exchange, HE) occurs, it often happens in the first polyploid generation, continues over subsequent generations, and then reduces in rate once meiosis becomes more stable and allopolyploids become established (Fig. 1g; Gaeta et al., 2007; Gaeta & Pires, 2010; Szadkowski et al., 2010; Xiong et al., 2011, 2021; Higgins et al., 2018; Chu et al., 2021; Wu et al., 2021). In HE, homoeologous segments reciprocally exchange materials resulting in what is often termed 'reciprocal homoeologous exchange' (Gaeta & Pires, 2010; Mason & Wendel, 2020). Due to independent assortment during gamete production or genetic drift and natural selection over evolutionary time, homoeologous exchange will appear to either maintain both subgenome copies of the exchanged region (Fig. 1d) or lose the copy from one subgenome while duplicating the retained subgenome in the exchanged region (Fig. 1e,f; Gaeta & Pires, 2010; Higgins et al., 2018; Mason & Wendel, 2020). The pattern of having one subgenome replaced by the other through an apparent deletion/

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Box 1 Glossary

Allopolyploidy – polyploidy when the parents are either from different species (taxonomic allopolyploidy) or genetically diverse (genetic allopolyploidy).
Amplified fragment length polymorphism (AFLP) – a PCR-based tool that selectively amplifies a subset of restriction enzyme-digested DNA fragments and detects the presence/absence of unique polymorphisms in the genomes of interest.
Aneuploid/unbalanced gametes – having more or fewer chromosomes than a complete set. This is a deviation from the total chromosome number being a multiple of the haploid set. A haploid set refers to a single, unique set of chromosomes from an organism.
Autopolyploidy – polyploidy when the parents are either the same species (taxonomic autopolyploidy) or genetically very similar (genetic autopolyploidy).
Biased fractionation – the asymmetric loss of duplicated genes following a whole genome duplication resulting in one subgenome having more retained genes than the other subgenome(s) in a polyploid genome.
Bivalent – when chromosome pairing involves alignment between a pair of homologous chromosomes.
Chimeric gene/fusion gene – a combination of coding sequences from different homologous and homoeologous genes.
Chromatin – a complex of DNA molecules and histone proteins that form chromosomes in eukaryotic cells.
Chromosome pairing – the coming together of homologous chromosomes in a genome forming alignment along the length of the chromosome. Most often referenced in the prophase of meiosis.
Chromosome segregation – the process of chromosomes being randomly sorted into daughter cells or gametes during mitosis and meiosis, respectively.
Crossing over – reciprocal exchange of large DNA sequences/segments between paired homologous chromosomes to repair DNA damage due to DSBs during meiosis.
Diploidization – the process in which a polyploidy genome returns to functioning as a diploid. The process includes changes in expression patterns, methylation, gene loss, and chromosome number reduction.
Disomic inheritance – regular chromosome pairing and segregation of alleles from each homologous chromosome into the gamete. This often refers to the pairing of homologous chromosomes from the same parent in an allotetraploid and the segregation of one homologous chromosome from each parent into the gamete.
DNA double-strand breaks (DSBs) – programmed formation of cell's self-induced breaks in DNA catalyzed by highly conserved topoisomerase-like SPO11 and other associated proteins to initiate meiotic recombination.
DNA methylation – a biological process involving the addition of a methyl (CH_3) group, often onto the fifth carbon of the cytosine residue of a DNA molecule.
Dosage-sensitive markers – molecular markers that can detect the variation due to loss or duplication of specific DNA fragments/copies compared with the expected total fragments in a specific genomic locus across the genomes of interest.
Fusion transcript – transcript resulting from a chimeric/fusion gene.
Gene conversion – a nonreciprocal swap of smaller DNA segments between chromosomes.
Genetic markers – DNA sequences with known physical locations on a chromosome.
H2A.Z – a highly conserved variant of histone protein H2A that plays a major role in different cellular processes.
Histone modifications – chemical modifications such as methylation, acetylation, phosphorylation, and ubiquitylation of specific histone proteins.
Homoeologous recombination/exchange – reciprocal exchange of genetic material between homoeologous (partially homologous chromosomes that share a common ancestor) chromosomes.
Homologous recombination – exchange of genetic material between homologous chromosomes.
Meiotic stability – the ability of a genome to maintain chromosome number through meiosis leading to viable gametes.
Multivalent – when chromosome pairing involves alignment between three or more chromosomes.
Nucleosome – a basic unit of chromatin that provides its compacted structure by wrapping a section of DNA sequence around a bundle of core histone proteins which is repeated across the genome.
Nucleosome occupancy – the positioning of nucleosome across the genome that determine the compactness and accessibility of DNA sequences.
Pangenome – represents the collection of entire sets of genes within a given species. The pangenome consisting of a core set of genes – present in all individuals of the species – and a dispensable set – genes that are present in some individuals in various copies and absent in others – represent the genetic diversity of the species.
Polyploidy – the state of an organism having more than two complete sets of chromosomes. Polyploidy ranges on a continuum of triploid – having three sets of chromosomes – to much higher orders.
Recombination – the process of chromosomes exchanging material reciprocally and nonreciprocally.
Restriction fragment length polymorphism (RFLP) – a dosage-sensitive marker that can detect the difference in the length (size) of homologous DNA fragments at restriction cut sites after treating/digestion of the given fragment with specific restriction enzymes.
Simple sequence repeat (SSR) – highly polymorphic simple tandem repeats of typically 1–6 nucleotides in length also known as microsatellites used for genotyping of individuals within and between species.
Single-strand conformation polymorphism (SSCP) – the difference in the conformation of single-stranded DNA sequences that allow them to separate distinctly from other sequences in gel electrophoresis.
Subgenome – a complete set of chromosomes derived from each parental species in an allopolyploid. The parental genomes are evolutionarily distinct bringing unique genomic and epigenomic features in allopolyploid species.
Synapsis – the pairing of chromosomes at the start of meiosis.
Syntenic chromosomes – evolutionary conserved gene order/content between chromosomes suggesting shared ancestry.
Whole genome duplication (WGD) – the doubling of genetic material equally across a genome. WGD is the base genetic mutation that leads to polyploidy.

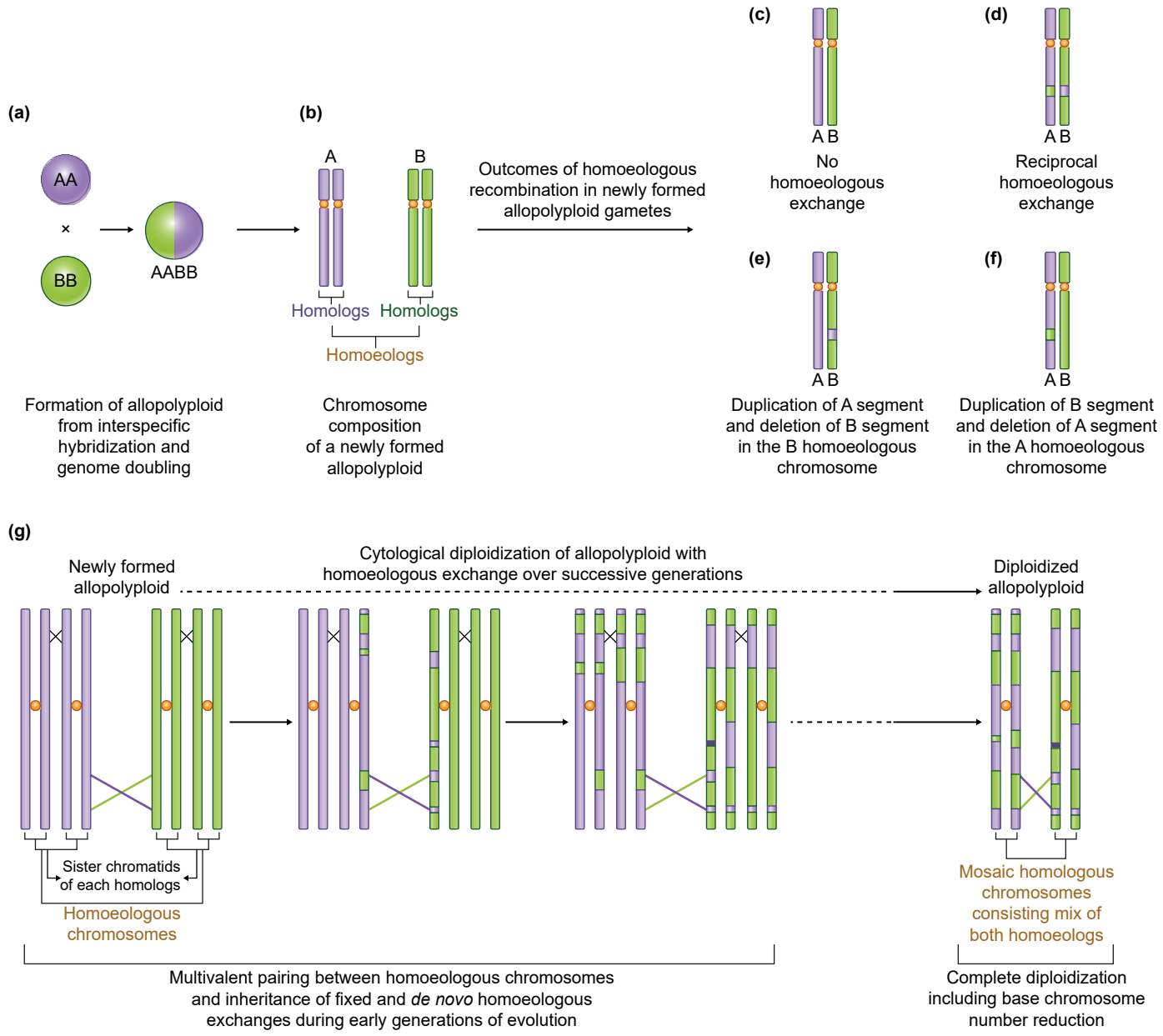

Fig. 1 Illustration of postpolyploidy cytological changes due to homoeologous chromosome pairing and recombination. (a) Species A and B exhibit divergent evolutionary histories and form allopolyploid species AABB after hybridization and genome doubling. (b) Allopolyploids contain both homologous – near identical; carry the sequence differences present in the diploid parents – and homoeologous – partially homologous; inherited into a single nucleus from divergent parental species who shared a common ancestor – chromosome sets. During the production of gametes post a single homoeologous recombination event, four possible pairings of homoeologous chromosomes will be found. (c) The most common pairing (9/16) would have no evidence of homoeologous exchange (HE) and represent distinct homoeologous chromosomes from both progenitor species. (d) The least common pairing (1/16) would exhibit reciprocal homoeologous exchange between A and B homoeologous chromosomes. (e, f) The remaining pairings have an equal probability of occurring (3/16) and represent the deletion of a homoeologous segment of one chromosome to be replaced with a duplication of the same segment from the other chromosome. (g) Homoeologous exchange can happen in the first generation after allopolyploid formation and continue over subsequent generations. Multivalent chromosome pairing and recombination will enable homoeologous chromosomes to swap genomic segments with each other. Subsequent generations will carry some of the fixed HEs from previous generations along with new HEs in each generation until the genome becomes more stable. Eventually, most of the allopolyploids retain diploid-like meiosis and reduce the rate of HEs. Over deep evolutionary time, allopolyploids become diploidized and may include base chromosome number reduction and complete restoration of diploid genetics. The diploidized genome carries the duplicated blocks of each subgenome and represents a mosaic-like structure consisting of a mix of homoeologous copies from both parental subgenomes.

duplication event is known as 'homoeologous exchange with replacement' (Gaeta & Pires, 2010; Edger et al., 2018; Higgins et al., 2018; Mason & Wendel, 2020). Homoeologous exchange is a fundamental evolutionary phenomenon bringing both negative – meiotic instability with unbalanced gametes and reduced fertility (Xiong et al., 2011) – and positive effects – novel genetic changes (e.g. gene presence/absence variation (PAV) and copy number variation (CNV)) with potentially diverse phenotypic outcomes –

during the establishment of allopolyploids (Z. He et al., 2017; Hurgobin et al., 2018; Bertioli et al., 2019; Zhang et al., 2020).

Historically, inferring genetic mechanisms is challenging when most data show a pattern and not a process. Early studies of postpolyploid evolution were often limited by genetic markers (e.g. simple sequence repeat; SSR or amplified fragment length polymorphism; AFLP) that could not differentiate a 'loss' from a 'loss and gain' of a homoeologous copy. While initial discoveries of homoeologous exchanges were made cytogenetically, it was not until the advent of dosage-sensitive markers (e.g. restriction fragment length polymorphism; RFLP or single-strand conformation polymorphism; SSCP) being used on mapping populations and resynthesized polyploids that one could show multiple observations of 'loss and doubling' occurring on multiple linked markers (e.g. allopolyploid Brassica napus; see Gaeta & Pires, 2010; Mason & Wendel, 2020; Zhang et al., 2020; Bayer et al., 2021; Ferreira de Carvalho et al., 2021). In the last decade, sequencing of numerous allopolyploid genomes revealed a significant number of historical fixed HEs, and population-level genomic data showed variation in HE occurrence within and between species (Chalhoub et al., 2014; Lashermes et al., 2014, 2016; Samans et al., 2017; Bertioli et al., 2019). By incorporating chromosome-scaffolded genomes, pangenomes (Hurgobin et al., 2018; Bertioli et al., 2019; Bayer et al., 2021), and long-read sequencing – whether for genome sequencing or transcriptomes – problems of uncertainty with copy number and presence/absence variation are becoming easier to overcome. We are now faced with the challenge of recognizing the potential complexity of homoeolog evolutionary history, given the prevalence of homoeologous exchange and our limited understanding of its impact on genome function (Edger et al., 2018).

Homoeologous exchange is a frequent and important aspect of the evolution and establishment of many nascent allopolyploids (Gaeta & Pires, 2010; Mason & Wendel, 2020). However, the occurrence of HEs varies within and between chromosomes, genotypes, and across generations of allopolyploid lineages. The mechanistic understanding of how HE frequency varies and the genomic consequences of these variations is still limited. Besides genome and chromosome level control, local-scale genomic and epigenomic features may potentially be important for understanding the mechanisms contributing to observed variation. Studying these aspects will facilitate fundamental insights into allopolyploid evolution. Furthermore, understanding the mechanisms of HE variation also has practical applications. Many crop species are allopolyploid (e.g. wheat, canola, cotton, coffee, peanut, strawberry, and banana), and correlation of HE with traits such as resistance to pathogens (Zhao et al., 2006), flowering time (Pires et al., 2004; Chalhoub et al., 2014), change in flower color (Bertioli et al., 2019), water use efficiency and seed yield (Raman et al., 2022), and salinity and hyperosmotic (drought-like) stresses (B. Wang et al., 2022) have been reported. Manipulating HEs to rearrange elite traits between parental subgenomes can benefit crop breeding practices. Current genomic and cytogenetic advances have yielded important insights into homoeologous recombination. In this review, we provide an overview of the observed patterns of HEs, characterize the putative genomic and epigenomic features associated with homoeologous recombination, and describe the genomic, phenotypic, and long-term evolutionary impacts of HEs. Lastly, we identify several important areas of research that need to be addressed in future studies to better understand the mechanistic basis and consequences of HEs.

II. Patterns of homoeologous exchange in allopolyploids

Owing to the high incidence of polyploidy found across angiosperm evolution and subsequently in major agricultural crops, homoeologous exchange has been primarily studied in plants compared with other taxonomic groups (see review in Grusz et al., 2017). Many advances in understanding the patterns of homoeologous exchange come from investigating natural allopolyploids though our knowledge of the short-term impact of HEs has been built through experiments with resynthesized allopolyploid lines (e.g. Brassica see Parkin et al., 1995; Sharpe et al., 1995; Pires et al., 2004; Udall et al., 2005; Gaeta et al., 2007; Szadkowski et al., 2010; Xiong et al., 2011, 2021). Although rare, homoeologous recombination has been reported in animals – mostly fishes and amphibians (Bi & Bogart, 2006; Allendorf et al., 2015; Grusz et al., 2017). Studies of cyprinid fishes show evidence of reciprocal homoeologous exchange in allotetraploid species (Cyprinus carpio-common carp and Carassius auratus-goldfish; J. T. Li et al., 2021) at rates of c. 3% of genes in each subgenome. HE has also been described in backcrossed allotriploid hybrids of these species (Ren et al., 2021). These studies did not explore instances of homoeologous exchange with replacement, which may be persistent in the genomes. Analysis of subgenomes in the allotetraploid frog Xenopus laevis found no evidence of large-scale recombination between homoeologous chromosomes (Session et al., 2016). The authors did find putative exchanges in repeat regions, though they were unable to rule out this as localized misassembly or errors in the assignment of repeat loci to subgenomes. Evidence of HEs has also been described in fungal species from the genus Saccharomyces, although detailed molecular investigations are limited (Usher & Bond, 2009; Grusz et al., 2017 and references therein). With the number of studies describing HEs in nonplant systems being low, there is a lack of data to infer HE patterns across diverse taxonomic groups leading our understanding of homoeologous exchange to be relegated to instances found in flowering plants.

Studies using cytological techniques, genetic markers, and other types of genomic data have identified trends in the frequency and occurrence of both homologous recombination (HR) and homoeologous exchange, allowing us to describe the similarities and distinctions between these two mechanisms (Gaeta & Pires, 2010; Grusz et al., 2017; Stapley et al., 2017; Zelkowski et al., 2019; Mason & Wendel, 2020; Zhang et al., 2020; Wu et al., 2021). Detailed investigations of HE patterns are limited to a handful of allopolyploid plant taxa such as natural and resynthesized B. napus, wheat, peanut, rice, and Tragopogon miscellus (e.g. Gaeta et al., 2007; Chester et al., 2012, 2013; Higgins et al., 2018; Bertioli et al., 2019; Zhang et al., 2020; Chu et al., 2021; Wu et al., 2021) though observations of HE in other lineages are abundant (e.g. quinoa and coffee; see Table 1). In this section, we

Table 1 Similarities and differences in the patterns of homoeologous exchange in selected allopolyploid species.

Species	Parental subgenomes	Ploidy	Reciprocal exchange/HE with replacement	Within chromosome distribution of HE	Uneven distribution between chromosomes	Subgenome bias in HE	Variation across individual accessions	References
Arabidopsis suecica	A. thaliana and A. arenosa	2n = 4x = 26	HE with replacement	Distal regions	Yes	A. thaliana subgenome is dominant	Yes	Zhang et al. (2020); Burns et al. (2021)
Arachis hypogaea (Cultivated Peanut) and A. monticola (Wild peanut)	A. duranensis (AA) and A. ipaensis (BB)	2n = 4x = 40	Both	Large blocks (distal regions); Small-scale gene conversion (throughout the chromosomes)	Yes	Larger blocks – AA subgenome is dominant; Small-scale gene conversion – BB subgenome is dominant	Yes	Bertioli et al. (2019)
Brassica napus (rapeseed/canola)	B. rapa (AA) and B. oleracea (CC)	2n = 4x = 38	Both	Distal regions	Yes	A subgenome is dominant	Yes	Chalhoub et al. (2014); Samans et al. (2017)
Cardamine flexuosa (Wavy Bittercress)	C. amara (CA genome) and C. hirsute (CH genome)	2n = 4x = 32	Only one reciprocal exchange event identified	Heterochromatic repeat-rich regions	Found between two chromosomes	Larger block translocated from CH to CA subgenome	Not known	Mandakova et al. (2014)
Chenopodium quinoa (Quinoa)	C. pallidicaule (A genome) and C. suecicum (B genome)	2n = 4x = 36	HE with Replacement	Distal chromosome arms	Found in only two chromosomes	A subgenome replaced the B subgenome segments	Not known	Jarvis et al. (2017)
Coffea arabica (Coffee)	C. canephora (C genome) and C. eugenioides (E genome)	2n = 4x = 44	Both	Large blocks (distal regions); single gene conversion (throughout)	Yes	E subgenome is dominant	Yes	Lashermes et al. (2014, 2016)
Fragaria ananassa (Cultivated garden strawberry)	F. vesca, F. iinumae, and two additional lineages	2n = 8x = 56	HE with replacement	Distal regions	Yes	F. vesca-like subgenome is dominant	Not known	Edger et al. (2019)
Miscanthus sinensis (Wild grass)	Not known. Putatively sorghum-like (n = 10) ancestor	2n = 2x = 38	Reciprocal	Distal regions	Found in only two chromosomes	No	Not known	Mitros et al. (2020)
Musa spp. (Bananas)	M. acuminata (A genome) and M. balbisiana (B genome)	2n = 3x = 33	Both	Mostly in the distal regions, some involved whole chromosome replacement	Yes	B subgenome is dominant	Yes	Baurens et al. (2019); Cenci et al. (2021)
Synthetic Oryza sativa (Rice)	subspecies japonica and indica	2n = 4x = 48	Both	Mostly distal regions. A few in the pericentromeric region	Yes	indica subgenome is dominant	Yes	Wu et al. (2021)

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Table 1 (Continued)

Species	Parental subgenomes	Ploidy	Reciprocal exchange/HE with replacement	Within chromosome distribution of HE	Uneven distribution between chromosomes	Subgenome bias in HE	Variation across individual accessions	References
Tragopogon miscellus	T.dubius and T. pratensis	2n = 4x = 24	Both	Distal regions	Yes	T. pratensis subgenome is dominant in gene conversion; no parental bias observed in whole chromosome loss or gain	Yes	Chester et al. (2012, 2013)
Synthetic allotetraploid wheat	Triticum urartu (AA) and Aegilops tauschii (DD)	2n = 4x = 28	Both	Distal regions	Yes	A subgenome is dominant	Yes	Zhang et al. (2020)

discuss the observed patterns of HEs – such as distribution along chromosomes and frequency across generations – based on these widely studied species. We also discuss evidence of homoeologous exchange in other allopolyploid species recently uncovered using large-scale sequencing projects (Table 1).

1. Population and individual level patterns

Variation in the presence/absence of specific HEs has been documented within and between populations of allopolyploids showing both fixed HEs from previous generations and de novo HEs unique to individuals. For example, resynthesized tetraploid lines developed by treating diploid hybrids of peanut's wild relatives (Arachis ipaensis × Arachis correntina) with colchicine showed homoeologous recombination in the initial tetraploid generation – S_0 generation – with unique events in each of the five analyzed S_0 plants (Chu et al., 2021). In the S_1 generation, each of the seven plants studied exhibited segregation of recombined segments found in S_0 along with novel S_1 HEs detected in three of the plants. The hybrids derived from crossing these synthetic tetraploid lines with cultivated peanut showed the inheritance of HEs from tetraploid parents to the F1 hybrids. Additionally, novel exchanges were identified in F1 hybrid populations. Established HEs from parental lines also showed disomic segregation in most F2 populations. Variable rates of de novo segmental chromosome duplication or loss, presumably due to homoeologous recombination or homoeologous associations, have been reported among the individuals of 10 testcross populations derived from diverse cultivated B. napus lines (Higgins et al., 2018). For instance, individuals from one of the lines (Surpass 400) were found to be the most stable, showing no evidence of HE. Conversely, two lines (Rainbow and PAK85912) were found to be highly unstable, with 22% of individuals having at least one HE event. Furthermore, all 254 individuals analyzed across all populations showed the presence of some fixed HE events identified in previous studies (e.g. Chalhoub et al., 2014; Z. He et al., 2017; Samans et al., 2017; Lloyd et al., 2018). Individuals of neo-allotetraploid Tragopogon miscellus, grown using field-collected seeds from different natural populations, showed evidence of variable HE events (Chester et al., 2012). The study detected HEs on at least one chromosome of 76% of sampled individuals across seven populations. Later, five representative T. miscellus individuals from this study were reanalyzed using an improved fluorescence in situ hybridization (FISH) technique (Chester et al., 2013). In each accession, all previously detected HEs were identified along with several additional small-scale exchange events confirming variation in de novo HEs across individuals. Analysis of HE events using natural and synthetic lines of commonly studied allopolyploids also suggests that the occurrence of HE can vary substantially among individuals within and between populations (Xiong et al., 2011, 2021; Lashermes et al., 2014, 2016; Baurens et al., 2019; Bertioli et al., 2019; Cenci et al., 2021; Wu et al., 2021).

2. HE patterns across generations

Homoeologous exchange – like other aspects of subgenome resolution in polyploids – likely has variable rates across lineages

and through generations (Gaeta et al., 2007; Szadkowski et al., 2010; Gou et al., 2018; Gaebelein et al., 2019; Wu et al., 2021). In the diploidization process, fractionation can occur in a few generations (Song et al., 1995; Xiong et al., 2011) though this process may be more prolonged due to relaxed purifying selection (Schnable et al., 2011; Cheng et al., 2012; Douglas et al., 2015). Similarly, rates of homoeologous exchange vary over generations (reviewed in Gaeta & Pires, 2010), which may be coincident with the patterns of nonbivalent chromosome pairing decreasing over time (Z. Li et al., 2021). Cytogenetic analysis of meiosis I chromosome pairing and segregation behavior of natural and resynthesized B. napus lines in both S_1 and S_{11} generations showed a decreasing rate of nonbivalent pairing from S_1 to S_{11} generations (Xiong et al., 2021). Although the difference across generations was not statistically significant within the resynthesized lines, there was a significant difference in rates compared with the domesticated accessions. Resynthesized lines showed a higher association between nonhomologous centromere sequences and 45S rDNA loci, potentially leading to high meiotic errors compared with natural lines. In synthetic wheat AADD tetraploids – produced by intergeneric hybridization between Triticum urartu (AA genome) and Aegilops tauchii (DD genome) followed by colchicine-mediated genome doubling – analysis of 1426 individuals in the S_{12} generation estimated the rate of HE events to be c. 0.1 per meiosis assuming a constant rate per generation (Gou et al., 2018; Zhang et al., 2020). This rate was argued to be likely lower than the actual rate, given that cytological identification of small-scale HEs is challenging (Zhang et al., 2020). High-resolution genomic data can detect more accurate rates of large- and small-scale HE events. By analyzing whole genome resequencing data (Wu et al., 2021), the rate of HEs in 202 euploid rice segmental allotetraploids – generated by colchicine treatment of the reciprocal F1 hybrids between two cultivars of japonica and indica subspecies – was described as 'polyploid-ratchet-like' a term used before to account for the rampant HE events in early generations of resynthesized B. napus lines compared with natural domesticated lines (Gaeta & Pires, 2010). Here, the rate of HEs per meiosis was 17.4 and 19.0 in the fourth and fifth generations, respectively (Wu et al., 2021). They argued that the higher rate of HE events might decrease in a few subsequent generations after the genome reached a certain threshold of homozygosity. Although most nascent allopolyploids lower the rate of HEs once the genome becomes more stable, the timing of acquiring robust pairing control and meiotic stability is uncertain. Some species exhibit nonbivalent pairing – and potential HE – after much longer periods of time, as observed in T. miscellus where after 40 generations, extensive chromosomal instability is still present (Chester et al., 2012). Available data suggest that nascent allopolyploids may undergo a prolonged period of extensive HEs and other chromosomal rearrangements before genome stabilization (Xiong et al., 2011; Chester et al., 2012).

3. Subgenome and chromosome level patterns

Homoeologous exchange also shows subgenome-specific bias – a feature unique to HE compared with HR. These patterns of subgenome bias are like patterns of subgenome dominance found in transcription, methylation, and paralog retention prominent during the resolution of subgenome function and diploidization (Edger et al., 2017; Bird et al., 2018; Alger & Edger, 2020). Analyses of the B. napus genome show that during HE, the A genome (derived from B. rapa) more frequently replaces C genome segments (derived from B. oleracea; Chalhoub et al., 2014; Samans et al., 2017). In octoploid strawberry, the Fragaria vesca-like subgenome is more likely to replace the three other subgenomes during HE resulting in an abundance of F. vesca-derived chromosome segments in the mosaic-like genome (Edger et al., 2019). As in other forms of subgenome dominance, the favoring of one subgenome over the other is not absolute and will vary across chromosomes and genetic loci (Grover et al., 2012; Edger et al., 2017, 2018; Bird et al., 2018). Within species, there is variation in which subgenome is dominant based on its chromosomal origin (Cheng et al., 2012; Murat et al., 2014; Bird et al., 2018; Alger & Edger, 2020). For instance, the F. vesca-like subgenome tends to be dominant during HE, but the extent of that dominance varies based on which another subgenome is being compared (Edger et al., 2019). As noted by the authors, this may have to do with the timing of the addition of these subgenomes, with the F. vesca-like subgenome being the most recent addition (Edger et al., 2019). In the peanut AABB genome, HE demonstrates variation in the directional bias of replacement based on the portion of a chromosome where the HE event occurs (Bertioli et al., 2019). Across multiple accessions, there is a bias toward the AA subgenome in the distal ends of the chromosomes. Proximal regions of the chromosomes demonstrate more accession-based variation in replacement though there is an overall trend toward the BB subgenome replacing segments of the AA subgenome. In addition to the placement on the chromosome, there is a noted difference in the size of HE segments, with those in the distal ends being large segments while the proximal regions are predominantly gene or exon-sized (Bertioli et al., 2019). Subgenome bias regarding HE can vary at the local genomic scale rather than being one subgenome dominantly replacing the other subgenome(s) throughout the entire genome.

Highly syntenic chromosomes are frequently observed to be more susceptible to HEs (Chalhoub et al., 2014; Lashermes et al., 2014, 2016; Samans et al., 2017; Higgins et al., 2018; Zhang et al., 2020; Wu et al., 2021). Most of the HE events in domesticated and resynthesized tetraploid B. napus lines are between A1/C1, A2/C2, and A9/C9 chromosomes, which are highly syntenic to each other (Chalhoub et al., 2014; Samans et al., 2017; Higgins et al., 2018; Lloyd et al., 2018). Observation of HEs in other chromosomes is rare. In Brassica allohexaploid hybrids, HE is also found between the most colinear chromosomes, as observed in allotetraploids (Gaebelein et al., 2019). Among the seven homoeologous chromosome groups in synthesized allotetraploid wheat, frequent HEs were reported in group 2 and 3 chromosomes, while other chromosome groups showed very little evidence of HE (Zhang et al., 2013, 2020). HEs in the newly established natural allotetraploid T. miscellus showed similar affliction to syntenic chromosome groups, which are found be a conserved pattern in populations of this species (Chester

et al., 2012). Among the six chromosome groups (A–F), group A chromosomes showed the highest frequency of HEs across individuals of all the populations analyzed in this study. Numerous studies found the preference of most colinear chromosomes for homoeologous exchange to be a common pattern across species (Nicolas et al., 2012; Bertioli et al., 2019; Edger et al., 2019; Gaebelein et al., 2019; Zhang et al., 2020; Wu et al., 2021).

4. Within chromosome and genic level patterns

Within chromosomes, the distribution of observed HEs follows a nonrandom pattern (Nicolas et al., 2012). Like trends of HR (Stapley et al., 2017; Zelkowski et al., 2019), HEs mostly take place in subtelomeric regions and are limited in centromeres and telomeres (Xiong et al., 2011, 2021; Nicolas et al., 2012; Jarvis et al., 2017; Burns et al., 2021; Kuo et al., 2021; Wu et al., 2021). An increase in HE events with increasing distance to centromeres was reported in a wide range of Brassica napus natural cultivars and resynthesized accessions (Samans et al., 2017; Higgins et al., 2018). Subtelomeric regions of these B. napus lines were found to become homogenized due to the duplication of a homoeologous copy from one subgenome and deletion of the other (Higgins et al., 2018). A similar pattern of HEs has been reported in peanut (as described above), synthetic wheat, Arabidopsis suecica, banana, and synthetic tetraploid rice (Zhang et al., 2020). However, exceptions to this common pattern are apparent as HE events were identified near the centromeres of HE-prevalent chromosomes in some species (Mandakova et al., 2014; Higgins et al., 2018; Wu et al., 2021). For instance, among the 129 de novo HE events identified in B. napus natural cultivar lines, 25 of them were found to be co-positioned with centromere locations (Higgins et al., 2018). In the euploid rice segmental allopolyploid, a higher frequency of HEs was observed in the pericentromeric regions of chromosome 1, while occurrences were lower in the subtelomeric region of chromosome 9 compared with equivalent regions in other chromosomes, which was not seen in patterns of HR (Wu et al., 2021). At the gene level, exonic sequences contain more HEs than intronic, intragenic, and noncoding regulatory elements (Zhang et al., 2020). Conversely, gene promoters and terminators are known to be hotspot regions of HR (Choi et al., 2013). Overall, HEs are found to be frequent in gene-dense regions in most studied allopolyploids using high-resolution genomic data (Zhang et al., 2020).

III. Genomic and epigenomic features associated with homoeologous exchange

Genetic control and sequence homology are two important determinants of homoeologous recombination (Gaeta & Pires, 2010). Pairing homoeologous 1 or Ph1 is a quantitative trait locus identified in hexaploid bread wheat (Riley & Chapman, 1958; Sears, 1977) and was found to promote recombination between homologous chromosomes. By promoting HR, this QTL is associated with a reduction in homoeologous recombination. Other loci that either suppress homoeologous exchange or promote HR have been described in Arabidopsis suecica (BOY NAMED SUE; Henry et al., 2014), wheat (Ph2; Mello-Sampayo, 1971), and Brassica napus (PrBn, BnaPh1; Higgins et al., 2021 and references therein). Suppression of HE due to dedicated genomic loci is not completely effective, as evidenced by the frequency of HE found in multiple allopolyploid genomes (Z. He et al., 2017; Higgins et al., 2018, 2021; Zhang et al., 2020). For a more comprehensive view of genetic controls of homoeologous recombination, see Cifuentes et al. (2010), Hollister (2015), Svacina et al. (2020), and Soares et al. (2021). Sequence similarity could explain the occurrence of extensive HEs in allopolyploids; however, this is not generalizable to all taxa. In coffee (Coffea arabica), both parental subgenomes are highly colinear, and all the homoeologous chromosome groups are found to be involved in HEs (Lashermes et al., 2016). Conversely, despite having colinear subgenomes, wavy bittercress (Cardamine flexuosa) has only one known reciprocal homoeologous exchange event (Mandakova et al., 2014). In teff (Eragrostis teff), subgenomes are highly syntenic along the entire length of homoeologous chromosomes, and coding regions show 93.9% sequence similarity (VanBuren et al., 2020) with no evidence of HEs. Current understanding of meiotic control genes and sequence similarity in allopolyploids is insufficient to conclusively explain the variation in non-HR frequency (Nyarko & Mason, 2021).

Variations in DNA sequence and epigenomic features from whole genome to fine-scale have been documented to be associated with variation in the rate of HR in eukaryotic taxa (Stapley et al., 2017), and given their overlapping similarity, it follows that this would also be true for homoeologous recombination. Recombination is governed at least in part by two primary genomic attributes: physical accessibility of cellular machinery to reach DNA and sequence similarity to serve as chiasmata (Mercier et al., 2015; Wang & Copenhaver, 2018). Openness of chromatin structure directly influences the ability of DNA strands to interact with each other or other protein complexes (Stapley et al., 2017; Wang & Copenhaver, 2018). Once chromatin is opened, methylation of DNA serves as another barrier of interaction through the blocking of DNA contact (Melamed-Bessudo et al., 2016; Wang & Copenhaver, 2018). Homologous recombination has been linked to gene-dense regions of chromosomes in part due to the prevalence of euchromatin and demethylated regions present to promote transcription (Brazier & Glemin, 2022). Genomic and epigenomic features have been used to predict the distribution of HR sites in different plant species. In diploid Arabidopsis inbred lines, recombination sites were predicted with more than 85% accuracy based on accessible chromatin, gene density, and DNA methylation (Lian et al., 2022). In a similar study, meiotic recombination sites of maize and Arabidopsis thaliana were predicted with high accuracy (> 90%) using genome sequence, chromatin, and chromosome location features (M. Wang et al., 2022). Homoeologous recombination shares pathways and molecular machinery with HR and may share similar genomic and epigenomic features (Table 2). In this section, we review aspects of the genome that can potentially contribute to our understanding of the molecular mechanisms influencing variation in homoeologous recombination.

Table 2 Comparison of genomic and epigenomic features associated with homologous and homoeologous recombination in selected species.

Recombination sites associated with:									
Chromosome features			DNA sequence features			Chromatin features			
	Gene density	Distance to telomere and centromere	Simple repeats/ TEs enrichment	G/C or A/T rich genomic regions	Reduced DNA methylation level	Histone modifications	Low nucleosome density	Chromatin accessibility	References
HR sites in Arabidopsis thaliana	Yes	Yes	A-rich motif (DSB and CO); CCN and CTT repeat motifs (CO)	A/T-rich regions	Yes	H3K4me1/2/3 (CO); H3K27me1(CO); H3K27me3 (DSB); H3K9me2 (CO and DSB)	Yes; including nucleosome with H2A.Z histone variant	Yes	Mirouze et al. (2012); Choi et al. (2013, 2018); Wijnker et al. (2013); Shilo et al. (2015); Zelkowski et al. (2019); Lian et al. (2022); M. Wang et al. (2022)
HR sites in Zea mays	Yes	Yes	GC-rich sequence motif (DSB); CCN/ CTT-like repeat motifs (CO)	G/C-rich regions	Yes	H3K9me2 (DSB); H3K4me3 (CO) H4K5ac (CO); H3K56ac (CO)	Yes	Yes	Y. He et al. (2017); Zelkowski et al. (2019); M. Wang et al. (2022)
HR sites in hexaploid bread wheat	Yes	Yes	A-rich motif; CCN-repeat motif; motifs related to TIR-Mariner and CACTA transposons	G/C-rich regions	Yes	H3K27me3	Yes	Yes	Haudry et al. (2008); Saintenac et al. (2011); Darrier et al. (2017); Tock et al. (2021); Higgins et al. (2022)
HR sites in rice	Yes	Yes	Stowaway and PIF/ Harbinger MITE transposons	G/C-rich regions	CG (Yes); CHG and CHH (opposite; showed enrichment in the crossover regions.)	H3K4me3, H3K9ac, H4K12ac, H3K27me3, H3K36me3	Yes	Yes	Muyle et al. (2011); Marand et al. (2019)
HE sites in tetraploid synthetic wheat	Yes	Yes	CCN-repeat motif	G/C-rich regions	Yes	Putatively positive association with euchromatin marks (e.g. H3K4me3); details not known	Yes	Yes	Zhang et al. (2020)
HE sites in Brassica napus	Yes	Yes	CT- or CTT- repeat motif; A-rich motif	G/C-rich regions	Yes	Putatively similar to wheat	Yes	Yes	Samans et al. (2017); Zhang et al. (2020)
HE sites in synthetic tetraploid rice	Yes	Yes	A-rich motif; CT- or CTT- repeat motifs; CCN-repeat motif	G/C-rich regions	Yes	Putatively similar to wheat	Yes	Yes	Li et al. (2019); Zhang et al. (2020)

CO, crossing over; DSB, double-strand break; HE, homoeologous exchange; HR, homologous recombination; TEs, transposable elements.

1. Chromatin structure

Similar to HR, a common pattern of HEs is their prevalence in subtelomeric regions and scarcity around centromeric and telomeric regions (e.g. Chen et al., 2018; Higgins et al., 2018; Bertioli et al., 2019; Zhang et al., 2020; Kuo et al., 2021; Wu et al., 2021). Chromatin structure could potentially impact such distribution patterns of both HR and HE. In many eukaryotic taxa, distribution of DNA double-strand breaks (DSB) and crossing over (CO) sites along chromosomes are reported to be influenced by chromatin structure in HR (Stapley et al., 2017; Zelkowski et al., 2019). Centromeres are localized with highly condensed heterochromatic regions of the genome (Mirouze et al., 2012; Stapley et al., 2017). Inaccessibility of recombination machinery (e.g. proteins associated with DSBs) might inhibit recombination in these regions (Wang & Copenhaver, 2018). Heterochromatic regions are highly repetitive due to the accumulation of transposable elements (TE) and are negatively correlated with recombination frequency as epigenetic suppression (e.g. methylation) of repeat elements is often directed to those regions (Mirouze et al., 2012; Choi et al., 2018). However, some organisms with few or no centromeric repeats also show lower recombination near the centromeres, which highlights that condensed chromatin structure potentially has a much greater impact on recombination rates relative to centromeres with high repeat density (Talbert & Henikoff, 2010; Stapley et al., 2017). Subtelomeric regions of chromosomes are usually characterized by high gene density and more open chromatin regions that might enable a higher frequency of DSB and CO formation (Choi et al., 2013; Shilo et al., 2015; Zelkowski et al., 2019). All examined eukaryotes show a positive association between euchromatin and recombination hotspots as these regions facilitate accessibility to recombination machinery (Choi et al., 2018; Zelkowski et al., 2019). Although rare, a few HE events have been identified near centromeres in B. napus (Higgins et al., 2018) and rice (Wu et al., 2021). Interestingly, rice did not exhibit HR near centromeres suggesting a possible mechanistic difference between HR and HE in this species (Wu et al., 2021). The mechanisms of these apparent exceptions of HEs to the common patterns of HR are likely to be variable across lineages and leave many questions in our understanding of the impacts of chromatin structure in HR and HE.

2. DNA methylation

Variation in methylation patterns of certain genomic regions is associated with recombination hotspots and cold spots. For example, HR hotspots in maize and Arabidopsis positively correlate with reduced levels of DNA methylation (Choi et al., 2013, 2018; Y. He et al., 2017; Kianian et al., 2018). Homologous and homoeologous recombination also share a positive correlation between reduced methylation and high recombination rate in other species (Table 2). Alteration of methylation patterns could result from interspecific hybridization and WGD (Song & Chen, 2015; Rigal et al., 2016; Edger et al., 2017; Li et al., 2019). In upland cotton, some genomic regions – mostly pericentromeric – are composed of large haplotype blocks where recombination is highly suppressed (i.e. recombination cold spots; Chen et al., 2020). Interspecific hybridization using different tetraploid species was found to increase the rate of recombination in low recombination regions of both homologous and homoeologous chromosomes. One key feature associated with the recombination rate changes in those cold spots was altered methylation patterns. Higher DNA methylation frequency at CG, CHG, and CHH sites was correlated with recombination cold spots, while the contrasting pattern was reported in recombination hotspots. In Arabidopsis, reduced CG methylation in pericentromeric regions increased the rate of DSBs while CO rates decreased (Choi et al., 2018). Conversely, reduced non-CG methylation (CHG and CHH sites) was found to be associated with both increased DSB and CO frequency, suggesting that methylation at different sites may have different effects in recombination frequency (Choi et al., 2018; Underwood et al., 2018). In addition to methylation impacting recombination through DNA accessibility, changes in methylation have been found to alter the expression of genes, directly affecting recombination rates (Mirouze et al., 2012). Repatterning of methylation is one of the first genome-level responses a newly polyploid organism undergoes in the process of reconciling subgenomes to function as one. The extent of repatterning is driven by the composition of the parental genomes (e.g. transposons; Edger et al., 2017) and ultimately influences the potential for homoeologous exchange.

3. Nucleosome occupancy and histone modifications

Local recombination hotspots are consistently associated with low nucleosome density and histone modification marks of euchromatin and facultative heterochromatin (Choi et al., 2013, 2018; Wang & Copenhaver, 2018; Lian et al., 2022; M. Wang et al., 2022). Common locations of recombination hotspots may vary across species, with some being prevalent in gene promoters or terminators while other species have them in gene bodies or intergenic regions (Zelkowski et al., 2019). In Arabidopsis, frequent HR observed in gene promoter regions is associated with low nucleosome density, higher levels of the H2A.Z histone variant, increased histone H3 lysine 4 trimethylation (H3K4me3), and lower DNA methylation levels (Choi et al., 2013). Several post-translational modifications of histones (e.g. methylation and acetylation) are found to be either in positive or negative association with recombination hotspots and can vary between their impact on DSB and CO across lineages (Table 2; Lian et al., 2022; M. Wang et al., 2022). For example, high levels of histone H3 lysine 9 and lysine 27 trimethylation (H3K9me3 and H3K27me3) and histone H3 lysine 9 dimethylation (H3K9me2) were found to be associated with Arabidopsis DSB sites. By contrast, H3K9me2 is associated with CO sites (M. Wang et al., 2022). In maize, a high level of H3K9me2 was also associated with DSB sites, while CO sites were associated with histone H3 lysine 5 and lysine 56 acetylation (H4K5ac and H3K56ac; M. Wang et al., 2022). However, none of these epigenomic features have been found to be uniquely associated with high DSB and crossover frequency (Choi et al., 2013; Lian et al., 2022; M. Wang et al., 2022). It was proposed that the interactions among features of chromatin, DNA

sequence, and chromosome organization might be able to explain variation in recombination activity in these hotspot regions (Choi et al., 2013). Models developed to predict the distribution of recombination sites showed that DNA methylation at CG and CHG sites, along with nucleosome occupancy, was able to predict crossover sites with > 90% accuracy in maize and Arabidopsis (M. Wang et al., 2022). Depleted nucleosome density, open chromatin regions due to active H3K4me3 euchromatin marks, and reduced methylation have also been reported to be potentially associated with homoeologous recombination sites in the synthetic tetraploid wheat, rice, and B. napus (Zhang et al., 2020). Although there is clear evidence that the hotspots of HR and HE share similar epigenomic features, hotspot sites are different in HE compared with HR (Zhang et al., 2020). While HR hotspots are preferentially gene promoters and terminators, HE hotspots are biased toward the gene body (Zhang et al., 2020). Higher sequence similarity in coding regions compared with regulatory regions might favor HEs to occur in the gene body and follows the pattern of genic regions having higher conservation than noncoding regions in homoeologous chromosomes (Zhang et al., 2020). It is essential to determine whether these molecular determinants of HE hotspots are common to most allopolyploids to understand the fine-scale molecular mechanisms of HE variation seen across different taxa (Tables 1, 2).

4. DNA sequence features

The positive correlation between GC content and HR rate is documented in many eukaryotes (Pessia et al., 2012). It is unclear, however, whether it is GC content driving an increase in recombination or vice versa. (Marsolier-Kergoat & Yeramian, 2009). Homologous recombination may drive increases in GC content putatively through the effect of GC-biased gene conversion during DSB repair in mammals (e.g. humans; Duret & Galtier, 2009) and plants (e.g. rice; Muyle et al., 2011). Conversely, in yeast (Saccharomyces cerevisiae), high GC content was found to positively affect the HR rate, although other genomic and epigenomic features are suspected to be involved (Petes & Merker, 2002; Marsolier-Kergoat & Yeramian, 2009). Homologous recombination is not always positively associated with GC content. In A. thaliana, HR is biased toward AT-rich regions compared with GC-rich regions (Wijnker et al., 2013). Interactions between GC-rich regions and chromatin states can influence the directionality of intergenomic gene conversion in allotetraploids (Guo et al., 2014). For instance, gene conversion from the A genome to the D genome in cotton (At Dt) is enriched in heterochromatic regions while conversion from the D genome to the A genome is enriched in the euchromatic chromosome arms (Guo et al., 2014). Enrichment in GC content follows the same pattern with the heterochromatic regions of the D genome and the euchromatic chromosome arms of the A genome containing relatively higher GC content compared with the other portions of the D and A subgenomes, respectively. GC content and chromatin state have been found to directly impact homoeologous exchange with HE-associated genes found mostly in euchromatic regions with higher GC content than other genes in resynthesized allotetraploid wheat (Zhang et al., 2020). The presence of lineage-specific variation in sequence bias of HR suggests that there is a need for similar investigations in homoeologous exchange, especially to determine shared and unique features between HR and HE.

The distribution of enriched simple repeat motifs (e.g. CCN, CTT, and A-rich motifs) is common between HR hotspots and HE-associated regions (Zhang et al., 2020). However, these motifs vary in frequency and level of enrichment among and within species, HR hotspots, and HE regions. In HR of Arabidopsis, only an A-rich motif was found to be enriched in DSB sites, whereas CO sites were enriched with CCN and CTT repeat motifs in addition to the A-rich motif (Shilo et al., 2015). These motifs are associated with nucleosome occupancy, H2A.Z and H3K4me3 euchromatin marks, and low DNA methylation (Shilo et al., 2015). Homoeologous recombination sites in synthetic tetraploid wheat showed enrichment of CCN-repeat motifs, while tetraploid B. napus showed enrichment of A-rich and CTT repeat motifs (Samans et al., 2017; Zhang et al., 2020). Repeat motifs in HR sites are found to be mostly enriched in gene promoters and terminators, while the same motifs are preferentially enriched in the gene body and are associated with homoeologous recombination (Zhang et al., 2020). Repeat elements of certain transposon families have also been found to be associated with HR hotspots (e.g. motifs related to TIR-Mariner and CACTA transposons enriched in hexaploid bread wheat (Darrier et al., 2017) and high enrichment of MITE transposons in rice (Marand et al., 2019)). The potential role of transposons in homoeologous exchange is currently untested. Given the prevalence of HE in gene bodies and the drastic consequences of TE insertion in genes, it may be that TE involvement is relegated to nongenic regions of the genome, is lineage-dependent, or does not impact HE in a significant way. Repeat motifs that promote recombination differ across lineages, and despite which motif it is, their presence or absence may be a predictive feature in determining overall rates of homologous and homoeologous recombination.

IV. Consequences of homoeologous exchange

1. Transcriptomic response

HE-induced genomic rearrangements may shuffle portions of homoeologs creating new combinations of parental genes and potentially contribute to transcript diversity and gene expression changes in allopolyploids (Kashkush et al., 2002; Tate et al., 2006; Gaeta et al., 2007, 2009; Koh et al., 2010). Lloyd et al. (2018) used tissue-specific mRNA-Seq datasets of B. napus to study the direct consequences of HE on gene expression. The magnitude of change in post-HE expression was found to be proportional to the differential expression of homoeologous genes especially when the products of those genes are dosage-dependent. Moreover, in cases of homoeologous genes with parental expression bias, duplication of one homoeologous copy was not always found to compensate for the expression level of the deleted homoeologous counterpart which may lead to altered total gene expression. If the parental homoeologous copies are functionally diverged, variation in total gene expression in the polyploid progeny may have potential

impacts on phenotypes (Pires et al., 2004; Chalhoub et al., 2014; Lloyd et al., 2018). Changes in total expression level – particularly for homoeologous genes with pre-existing parental expression bias – was reported in synthetic wheat (AADD) tetraploids (Zhang et al., 2022). Strong HE effects on gene expression and alternative splicing were also observed in synthetic rice segmental allotetraploids (Zhang et al., 2019). Here, 70–82% of the genomes became homogenized in the S_{10} generation due to HEs, and most of the genes in these regions retained parental expression levels while only a few were differentially expressed. Genes with expression levels similar to parental genomes are putatively under cis-regulation (e.g. promoters and enhancers) while differentially expressed genes are controlled by trans-regulatory factors (e.g. transcription factors). However, they did not rule out the possibility that repatterning of DNA methylation in earlier postpolyploid generations might influence differential gene expression. Due to interacting evolutionary processes – hybridization, WGD, and associated postpolyploidy changes such as biased fractionation, methylation repatterning, and variation in TEs – establishment of a direct causal relationship between HE and divergent transcriptomic response is not straightforward (Osborn et al., 2003b; Edger et al., 2017; Bird et al., 2018, 2021). Investigation of HE-induced transcriptomic response requires systematic analysis to uncouple the impacts of HE from other confounding factors of the diploidization process.

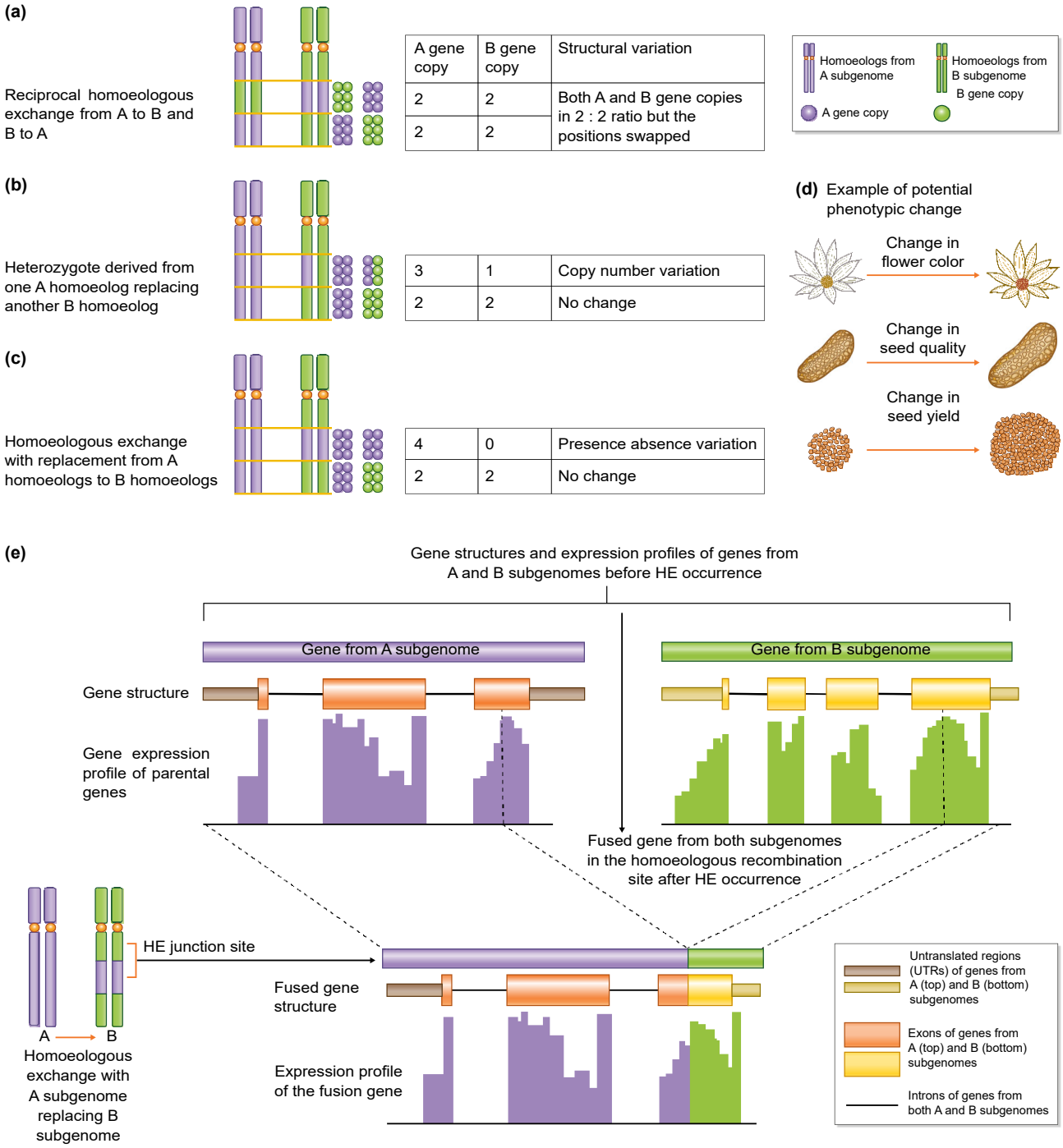
2. Structural variation and novel phenotypes

Structural variations (SVs) are large-scale – > 50 base pairs to over several megabase pairs in size – genetic differences between individuals which include insertions and deletions, CNV, translocations, and inversions of chromosomal regions (Gabur et al., 2019, 2020; Yuan et al., 2021). Owing to their size, SVs have a comparatively higher potential to alter gene dosage, change gene structure, create positional effects, and perturb function (Fuentes et al., 2019). Among various recombination- and replication-based cellular mechanisms (Hastings et al., 2009; Gabur et al., 2019 and references therein), homoeologous exchange can also lead to genomic SV. Reciprocal homoeologous exchange could swap the genes and chromosome segments between the subgenomes (Fig. 2a) with no apparent loss or duplication from either subgenome (Schiessl et al., 2019). Conversely, the presence of heterozygotes due to the segregation of a parentally derived and fixed reciprocal exchange event in one individual and absence in the others could give rise to CNV between individuals (Fig. 2b; Schiessl et al., 2019). In Fig. 2(b), this results in three copies of subgenome A (purple) and one copy of subgenome B (green), though one of the copies of subgenome A has now moved. In addition, duplication-deletion events which involve the duplication of homoeologous genes/segments from one subgenome and deletion of the other in the exchanged regions may lead to presence–absence variation – a particular form of CNV (Fig. 2c; Hurgobin et al., 2018). In both HE-induced CNV and PAV, HE alters the 2 : 2 homoeologous ratio from each subgenome keeping the overall gene content static but changing the composition of homoeologs: CNV (1 : 3, 3 : 1) or PAV (4 : 0, 0 : 4).

HE-induced SVs have been linked to diverse phenotypic changes (Fig. 2d) in many allopolyploids such as B. napus (Stein et al., 2017; Hurgobin et al., 2018), wheat (Gou et al., 2018; B. Wang et al., 2022), tobacco (Nicotiana tabacum; Shi et al., 2022), and peanut (Bertioli et al., 2019). Genetic mapping of synthetic B. napus revealed segmental duplication and deletions of homoeologous regions and linked them as underlying mechanisms of trait variation – for example, HEs in the QTL region known for affecting seed quality traits (Liu et al., 2012; Stein et al., 2013, 2017) and flowering time (Pires et al., 2004). The association between PAV and HEs has also been described in the early generations of B. napus synthetic accessions (Hurgobin et al., 2018). The spontaneous change in flower color from yellow to orange in some lineages of synthetic allotetraploid peanut has been linked with HE-induced genetic changes (Bertioli et al., 2019). It was shown that the alleles from the A subgenome that confer yellow color are replaced by the alleles from the B subgenome that confer orange color (Bertioli et al., 2019). In tobacco, allelic variation in a QTL region potentially due to HE-induced duplication-deletion events was observed to be correlated with partial resistance to soil-borne pathogens (Shi et al., 2022). In multiple studies, the association between HE and important agronomic traits such as flowering time, defense, and metabolism (Hurgobin et al., 2018 and references therein) was identified which consistently indicates HE as a major cause of genomic SV in allopolyploids that could create diverse phenotypic outcomes.

Besides phenotypic outcomes due to the alteration of parental homoeolog ratios, the positions of HE-induced structural variant

Fig. 2 Examples of genome and gene level effects of homoeologous exchange (HE). In the top section of the figure, yellow lines represent the homoeologous regions with and without HEs and their respective gene copies are depicted with purple and green circles. Structural variation due to HEs and the associated changes in gene copies are shown in the tables. (a) Reciprocal homoeologous exchange and inheritance of both recombined segments in the subsequent progenies result in no apparent loss from either subgenome copies. Although the A and B gene copies maintain a 2 : 2 ratio, the position of the genes has changed. (b) Exchanges between homoeologous segments of A and B subgenomes may result in a heterozygote. The maintenance of the homoeolog replacement in subsequent generations of some individuals and loss in others may change the homoeologs ratio from 2 : 2 to 3 : 1 and will create copy number variation (CNV) between the individuals. (c) Similar to CNV, presence/absence variation (PAV) could also result from a homoeologous exchange with replacement. Here, homoeologous pairs of the A subgenome deleted and replaced both the B homoeologous pairs resulting in four copies of A homoeologs and none of the B homoeologs in the exchanged region. (d) Potential phenotypic outcomes such as changes in flower color or seed quality traits (e.g. seed color and fiber content, glucosinolate content; Stein et al., 2013, 2017; Hurgobin et al., 2018) could result from PAV and CNV. (e) The presence of HE junction sites within a single exon may generate fused, or chimeric, genes combining coding regions of genes from both parents resulting in a fusion transcript. The fusion transcripts could either be differentially expressed or at a similar (shown here) expression level compared with parental gene expression and potentially result in phenotypic changes.



sites could have potential effects on the regulation of gene expression and resulting protein structure and function (Fig. 2e; Zhang et al., 2020). For instance, exchanges in 5^0 regulatory regions may result in the regulation of genes on one subgenome by regulatory proteins encoded by the other subgenome. The changes in enhancer–promoter interactions would potentially result in novel transcriptional regulation and thereby expression changes. It is also possible that exchanges in the open reading frame or in the HE junction in 3^0 untranslated regions of a gene could result in differences in protein folding or post-translational regulation with

respect to the parental copy which may either generate novel function or deleterious effects. Recent work in wheat (Zhang et al., 2020) identified intragenic HE junction sites that result in recombinant fusion transcripts and argued HE as an important mechanism of postpolyploidy neo- and subfunctionalization. Detailed investigation of identifying such chimeric genes and functional annotation of these fusion proteins in other polyploid lineages would broaden the understanding of HE-induced phenotypic innovation.

3. Subgenome dominance

Homoeologous exchange with replacement is often found to be biased toward one subgenome and has been reported frequently in many allopolyploids (Chalhoub et al., 2014; Samans et al., 2017; Bertioli et al., 2019; Edger et al., 2019). Biased retention of segments and genes from one subgenome to the other during HE will result in an asymmetric representation of parental genomes in the exchanged regions (Mason & Wendel, 2020). This subgenome bias will potentially result in more gene retention from one of the parental genomes and loss from the other genome (e.g. maize (Schnable et al., 2011) and strawberry (Edger et al., 2019)). Consequently, overall gene expression from the more highly retained genome will contribute more to the overall expression and function of the full genome. Biased homoeologous exchange with replacement could act as one of the major causes of subgenome dominance – a frequently observed postpolyploidy mechanism of allopolyploid evolution (Bird et al., 2018; Alger & Edger, 2020; Z. Wang et al., 2022). Subgenome dominance is described in many allopolyploids – for example, maize, Brassica, strawberry, and Mimulus (Bird et al., 2018; Alger & Edger, 2020; Z. Wang et al., 2022). However, in many allopolyploids, homoeologous exchange was not considered, so the link between subgenome dominance and HE is still speculative (Edger et al., 2018). The consequences of subgenome dominance in allopolyploids and hybrids are extensive and have agricultural, ecological, and evolutionary implications (Bird et al., 2018). The identification and use of homoeologous exchange in defining subgenome dominance will properly account for the contribution of each parental subgenome in allopolyploid genome function, establishment, and evolution.

4. Changes in long-term evolutionary history

Over deep evolutionary time, extensive homoeologous exchange leads to a mosaic-like genome structure of the diploidized allopolyploids which could blur the distinct history of each subgenome (Edger et al., 2018). HE events could create chimeric genes or segments or result in gene loss. Incorporating those genes or segments into phylogenetic analysis might exhibit convoluted phylogenetic signals which will complicate locus-specific evolutionary history. The absence of HE or the presence of reciprocal HE would show polyploid subgenomes as closely related to each of their respective parental lineages (Fig. 3a,b). However, reciprocal exchange will change the locations of the segments placing them on chromosomes from the alternative parent. In such cases, analysis of conserved gene order in association with phylogenomic analysis will demonstrate HE in each locus while identifying the correct evolutionary relationships (Edger et al., 2018). Conversely, HE with replacement would change the evolutionary history of the deleted segments. The duplicated segments would represent the evolutionary signal of only one subgenome and mask the other. As a result, both homoeologous copies will be more closely related to each other than to either parent though the copies will be more closely related to one parent over the other (Fig. 3c). Phylogenomic analysis including HE junctions or chimeric genes is susceptible to confounding phylogenetic signals. These signals will result in different topologies based on the portion of the gene or segment used and in the case of the whole gene or segment may return relationships that do not depict the true history of the subgenomes (Fig. 3d,e). Such changes in subgenome evolutionary history can be easily detectable in newly formed allopolyploids or those with known progenitor species. However, it is very difficult to separate the correct phylogenetic signal in natural ancient allopolyploids with extinct diploid progenitors or parental relatives. If homoeologous exchange is a common phenomenon immediately after allopolyploid formation, then it is imperative to consider phylogenomic history when interpreting different postpolyploidy mechanisms of diploidization.

V. Conclusion and future directions

Homoeologous exchange influences the evolution of allopolyploid species. The rate of HE varies among individual lineages, between generations, and across species. The genetic mechanisms that control the rate of HEs have thus far been most extensively studied in wheat and Brassica leaving an open field of exploration across angiosperm diversity. Identifying the HE-controlling locus (e.g. Ph1) and candidate meiotic genes in those regions (Higgins et al., 2021; Kuo et al., 2021; Zhang et al., 2023) in more species would elucidate why certain species have higher rates of HE compared with others. This knowledge could be useful in manipulating recombination in polyploid species and enhancing the practical application of introgression from wild relatives to crop species (Taagen et al., 2020; Hu et al., 2021). Consideration of the rate and patterns of HE in subgenomes is essential in studying postpolyploidy genome evolution. Gaining an improved understanding of which HEs were favored or under positive selection will help in identifying stabilizing HEs and regions encoding genes that contribute to favorable phenotypes. Identifying where events occur, estimating rates, and understanding the controlling mechanisms of HE could benefit from using high-throughput next-generation sequencing data alongside conventional genetic, biochemical, and cytological approaches (e.g. Zhang et al., 2020; Wu et al., 2021). Application of single-molecule (SM) and super-resolution (SR) optical approaches have contributed to new insights into HR by providing high spatial and temporal resolution of structural features and molecular mechanisms during meiosis (reviewed in Kaniecki et al., 2018). Alongside oligo-based FISH techniques (Braz et al., 2018), SM and SR approaches would be important technological avenues to explore to investigate homoeologous recombination in unprecedented detail.

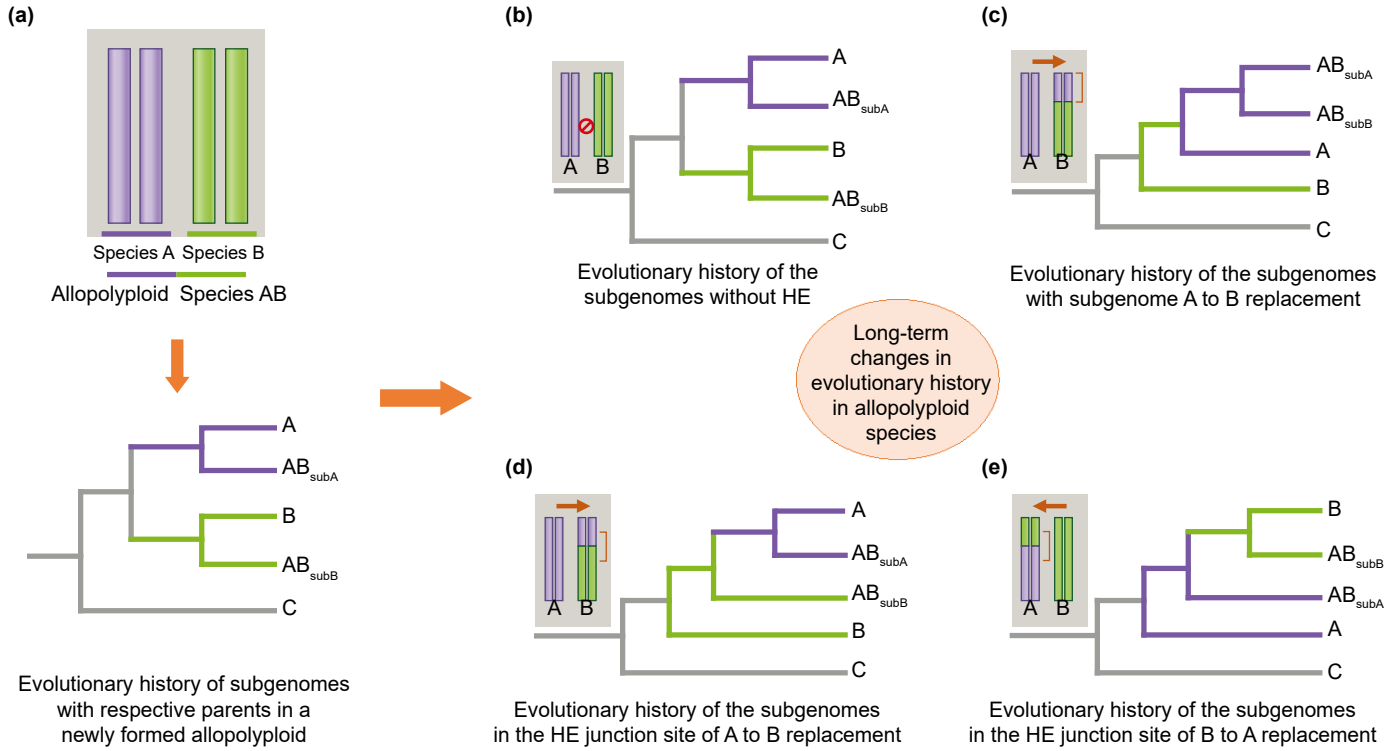


Fig. 3 Putative long-term effects of homoeologous exchange with replacement in the evolutionary history of allopolyploid species. Only a few putative scenarios are depicted here. (a) Species A and B are hybridized and coupled with a whole genome duplication resulting in allotetraploid species AB. AB_{subA} and AB_{subB} are used to represent the subgenomes of the polyploid species AB. A and B are parental genomes and C is an outgroup used to anchor the tree. The phylogeny of a newly formed allopolyploid shows that the AB_{subA} subgenome is closely related to the A parental genome, and the AB_{subB} subgenome is closely related to the B parental genome. (b) The absence of homoeologous exchange does not affect the evolutionary history of AB_{subA} and AB_{subB} subgenomes to their respective parents. (c) Subgenome AB_{subA} replaces AB_{subB} (the orange arrow shows the direction of replacement) in the bracketed (orange) portion of the chromosome. In the phylogenetic tree, both subgenomes are more closely related to each other compared with their parental lineages. As a clade, they are most closely related to the parent subgenome of origin. (d, e) Depending on the individual contributions of each subgenome to the genomic segment used for phylogenetic reconstruction, the history of the chimeric segment or gene can have varying signals.

Studying higher-order genome organization and epigenome profiling of HE junction sites would provide a robust mechanistic understanding of homoeologous chromosome pairing, diploidization, and evolutionary novelties generated during the process. Specific sequence motifs, methylation patterns, or the presence of specific histone proteins and their modifications enable chromatin in certain sites to become more accessible for HEs to occur than in other sites (Zhang et al., 2020). Some allopolyploids are subject to extensive HEs while others show very little to no HE. How these species differ in 3D genome structure and epigenome profiles would help us to identify other molecular mechanisms besides genetic factors that control or impact the pairing of homoeologous chromosomes. This mechanistic understanding would also potentially explain the evolution, establishment, and regulation of HE-induced gene conversions (e.g. fusion genes) and their phenotypic outcomes. Understanding molecular regulatory mechanisms of chromosome pairing behavior in polyploids has far-reaching implications, including improving the fertility and target traits of polyploid crops. Our understanding of the molecular mechanisms of how HE results in such outcomes remains limited. Characterization of these mechanisms has the capacity to translate directly to the improvement of multiple polyploid crop species due to the integration of HE-inspired genetic engineering (Zhang et al., 2023).

Knowing the evolutionary history of polyploids is essential to understand the mechanisms of the diploidization process including subgenome dominance and biased fractionation (Edger et al., 2018). Knowledge of evolutionary history will distinguish whether postpolyploidy changes (i.e. gene retention/loss, biased fractionation, and subgenome dominance) are attributable to inherent differences in the parental genomes or due to other mechanisms, an aspect of polyploid evolution of which we still understand very little. Extensive HE between subgenomes resulting in a mosaic-like genome adds more to this complexity (Hardigan et al., 2021). It is often very difficult to accurately identify the extent of HE in ancient allopolyploids which can be attributed to unknown parental ancestry of polyploid species. It is possible that the diploid progenitors of an ancient polyploid event are extinct, or through extensive chromosomal rearrangement, variable selective pressure, and differences in accumulated mutations between homoeologs, phylogenetic signal showing their relatedness has been obscured. In such cases, identification of fine-scale HEs between subgenomes using phylogenomic methods and including extant parental relatives in the analysis would potentially enable

better characterization of diploidization processes including subgenome dominance (Edger et al., 2018).

Continued advances in sequencing technology have led to unprecedented investigations into both the depth of genomic diversity within species (pangenomics) and the unraveling of complex genomes previously considered too difficult and costly to sequence. Polyploid genomes have been ideal tests of the capacity of current technology given their innate difficulty in sequencing as well as their overall importance to economics and agriculture. Having chromosome-scale and phased polyploid genome assemblies as part of future studies using long-read sequencing technologies and improved bioinformatics algorithms will be highly advantageous to gain a deeper understanding of homoeologous recombination and polyploid genome evolution in general (Blischak et al., 2018; Edger et al., 2018; Mason & Wendel, 2020). The incorporation of single molecule and super-resolution optical microscopy would facilitate unprecedented discoveries in postpolyploidy cytological phenomena leading to our deeper understanding of the evolution of polyploids.

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Competing interests

None declared.

Author contributions

SKD and MRM planned and designed the research. SKD, PPE, JCP and MRM wrote the manuscript.

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