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Genomic and Expression Plasticity of Polyploidy

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Abstract

Polyploidy or whole genome duplication (WGD) occurs throughout the evolutionary history of many plants and some animals, including crops such as wheat, cotton, and sugarcane. Recent studies have documented rapid and dynamic changes in genomic structure and gene expression in plant polyploids, which reflects genomic and functional plasticity of duplicate genes and genomes in plants. Common features of uniparental gene regulation and nonadditive gene expression in regulatory pathways responsive to growth, development, and stresses in many polyploids have led to the conclusion that epigenetic mechanisms including chromatin modifications and small RNAs play central roles in shaping molecular and phenotypic novelty that may be selected and domesticated in many polyploid plants and crops.

Keywords

polyploidy; paleopolyploidy; crops; nonadditive gene expression; small RNAs; epigenetics

Polyploid events

Every plant sequenced to date has a repertoire of duplicated genes that arose via segmental duplications, transposition, tandem gene duplications or polyploidy. Here we focus on polyploidy—duplication of an entire genome. Recent estimates indicate that 15% of angiosperm and 31% of fern speciation events are accompanied by ploidy increase [1]. The proportion of polyploidy in flowering plants may be over 70%, and the majority (>75%) are allopolyploids [2]. Polyploids are generally divided into two categories: autopolyploids, duplication of the same genome; and allopolyploids, merging of two diverged genomes into a common nucleus. These distinctions are unclear in paleopolyploids.

The impact of polyploidy on species numbers and diversification and its contribution to adaptive and ecological fitness has been debated [1,3]. Moreover, processes governing post-duplication genomic restructuring remain abstruse although collectively referred to as diploidization (Figure 1) [4]. Determining the success of a polyploidy event is complicated partly because some lineages have experienced recurrent polyploidy events (*Glycine*, for

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example [5]). Moreover, nucleotide substitution rates can vary between lineages, even within a genus [6], complicating dating of shared duplications. Some duplicated segments show signs of concerted evolution that may confound phylogenetic conclusions. These processes can complicate dating and placement of ancient duplication events [3,7,8].

Some polyploid genomes have highly fractionated duplicated segments due to asymmetric and stochastic gene loss [7,9]. An interesting comparison will be between the genomes that share roughly contemporaneous duplication events. For instance, the last duplication event in soybean and maize was approximately 10-15 million years ago (Mya) [10,11] and would make an interesting comparison of gene retention, although abundant transposable elements (TE) in the maize genome might affect post-duplication genomic restructuring.

With the influx of sequenced genomes, it is possible to compare and contrast duplication events in plant genomes that share a) the same duplication event but have since diverged, b) contemporaneous duplication events but in different lineages, and c) multiple duplication events in the same genome. The rules governing post-duplication genome evolution may be determined by studying such systems. However, the only rule may be that there is no rule and that each event is independent and in its own unique context.

Genomic plasticity and evolution in polyploids

New polyploids have disadvantages in reproduction [12]. Prezygotic hybridization barriers may prevent the formation of interspecific hybrids and allopolyploids [13] (Figure 1). The mechanisms of the prezygotic barriers are unknown, but may result from pollen-stigma incompatibility. Postzygotically, increasing genome dosage may serve as a genome-wide mutagen, altering the balance between regulatory interactions and gene expression networks [9,14]. Autopolyploids have to overcome the odds of random chromosome segregation during meiosis. This is why some autopolyploid plants cannot produce many seeds, and triploids are seedless. To avoid reproductive failures, some interspecific hybrids and polyploids may also develop asexual reproduction such as apomixes [15].

In allopolyploids, chromosome pairing occurs primarily between homologous chromosomes and rarely between homoeologous chromosomes derived from different species. The degree of homoeologous chromosome pairing may be inversely related to the genetic distance between the progenitors: the greater the genetic distance, the less likely that interspecific hybrids and allopolyploids will be formed, and the reduced likelihood of homoeologous chromosome pairing. For example, A- and D-genome progenitors of allotetraploid cotton diverged 7-8 Mya. In allotetraploid cotton, most genetic loci are additive, and homoeologous genes evolve independently, relative to the progenitors [16]. Likewise, in resynthesized allotetraploids formed between *A. thaliana* and *A. arenosa* that diverged 5-6 Mya [17], there is little evidence for genomic changes [18,19], and *A. suecica* natural allotetraploids are genetically trackable. In *B. napus*, the progenitors *B. rapa* and *B. oleracea* diverged ~3.5 Mya and are closely related [20]. As a result, numerous chromosomal rearrangements are documented in resynthesized *Brassica* allotetraploids [21]. This high level of genomic changes may also be attributed to genetic factors such as *PrBn* that promotes homoeologous pairing [22]. In hexaploid wheat, although the A-, B-, and D- progenitors diverged 2-3 Mya [23], pairing rarely occurs between homoeologous chromosomes, due mostly to *Ph1* that suppresses pairing of homoeologous chromosomes [24]. Rapid genomic changes are also observed in *Tragopogon* allotetraploids [25], derived from diploid progenitors that diverged ~2.5 Mya (D. E. Soltis, personal communications). A divergence of 5-6 million years between progenitors may be required to form stable allopolyploids. If the progenitors are closely related, the resulting allopolyploids may undergo a rapid process of diploidization. Both diploidization and disomic chromosome pairing facilitate the evolution of newly formed allopolyploids.

Nonadditive gene expression changes and functional plasticity in allopolyploids

It is predicted that duplicate genes gain new function via neofunctionalization and/or diverge from the ancestral function through subfunctionalization [4]. This may not explain the situation in which some homoeologous genes are silenced or activated in allopolyploids, but the functions are maintained over time. For example, expression of uniparental rRNAs is common in many interspecific hybrids and allopolyploids [26]. Moreover, gene expression changes are not neutral; there is an expression hierarchy of rRNA genes: *B. nigra* > *B. rapa* > *B. oleracea* in three *Brassica* allotetraploids [27]. This expression bias is also observed for many protein-coding genes, and 60-94% of the repressed genes in the *Arabidopsis* allotetraploids are of *A. thaliana* origin [19,28]. Thus, at least part of gene expression variation in allopolyploids is controlled by non-Mendelian or epigenetic mechanisms [13] (Figure 1).

A general trend of additive and nonadditive gene expression in allopolyploids

If gene expression is additive, the expression value of a gene in a tetraploid is equal to 2 or mid-parent value (MPV) ($1 + 1 = 2$; alternatively, $0.5\text{Parent1} + 0.5\text{Parent2} = 1$). If a gene is nonadditively expressed, the value of the gene in the tetraploid is either larger or less than 2 ($1 + 1 > 2$ or $1 + 1 < 2$). The expression value would be 1, when one of the parental loci is completely silenced, and 0, when both parental loci are silenced. Nonadditive gene activation and repression suggests positive and negative dosage effects on gene expression in polyploids, respectively.

Genome-wide gene expression studies in a variety of allopolyploids including *Arabidopsis*, cotton, *Senecio*, and wheat reveal a trend of additive and nonadditive gene expression. The proportion of additively expressed genes varies from 65-95% in *Arabidopsis* allotetraploids [28], 30-70 % in cotton allotetraploids [29], 40-73% in *Senecio* interspecific hybrids and allohexaploids [30], to ~80% in synthesized wheat allohexaploids [31]. Additive expression for a large number of genes may provide a molecular basis for dosage balance and compensation of functionally redundant genes [14], leading to developmental stability in new allopolyploids.

Nonadditively expressed genes include ~16% in wheat allohexaploids [31], 30-70% in cotton allotetraploids [32], 30-60% in *Senecio* allohexaploids [30], and 5-38% in *Arabidopsis* allotetraploids. [28]. Nonadditive expression of the genes encoding transcription and regulatory factors may reprogram gene expression networks and nonadditive phenotypes in allopolyploids.

The extent of nonadditive expression at mRNA and protein levels has not been directly compared. Albertin et al. [33] showed nonadditive accumulation of >25% of ~1600 polypeptides measured in resynthesized *B. napus* allotetraploids. However, the overall distribution of the protein functional categories and metabolic pathways is not substantially altered in the allotetraploids relative to the parents.

Greater effects of hybridization than genome doubling on nonadditive gene expression

Nonadditive expression may result from genome merger (hybridization between the species) or genome doubling (dosage increase) in the allopolyploids. To discern these effects, Hegarty et al. [30] compared gene expression differences between allohexaploids and synthetic interspecific triploids. The number of nonadditively expressed genes in the triploids is twice the number in the allohexaploids, whereas the number of additively expressed genes is nearly the same. Similarly, ~76% of biased homoeolog expression events found in the F_1 interspecific hybrids are not present in a natural allotetraploid (*Gossypium hirsutum* L.) [29]. The data

suggest larger effects of hybridization than genome doubling on nonadditive gene expression. Moreover, ~25% of differentially expressed transcripts between the triploids and allohexaploids tend to share the patterns with those in the natural allopolyploid [30], consistent with stochastic and directional activation or silencing of rRNA genes [26] and protein-coding genes [19].

Nonadditive gene expression is a feature of parental dependent repression or activation in allopolyploids

In resynthesized and natural allotetraploids [18,19,28] that involve *A. thaliana* and *A. arenosa*, non-additive repression of gene expression is primarily associated with the *A. thaliana* homoeologous genome; this observation is consistent with siRNA accumulation and DNA methylation of *A. thaliana* centromeres in the allotetraploids [34]. In a synthetic allohexaploid wheat line [35], 7.7% of transcripts displayed nonadditive expression, and >95% of the differentially expressed transcripts are reduced or absent in the allohexaploid. In cotton allotetraploids, the expression of homeolog-specific expression can be biased toward A- or D-genome species. Flagel et al. [29] concluded that there is a tendency of expression bias toward the genes of the fiberless D-genome species, while Yang et al. [36] observed that many of the ESTs are enriched during early stages of fiber development are derived from the A-genome species that produces fibers.

A molecular clock model of nonadditive gene expression in allopolyploids

Many genes involved in photochrome signaling, chlorophyll biosynthesis, and starch metabolism are upregulated in *Arabidopsis* allotetraploids [28], and some are nonadditively expressed in *Brassica*, *Senecio*, and wheat allopolyploids [30,31,33]. Upregulation of these genes is controlled by several transcription factors in the feedback regulation of circadian clocks. Specifically, during the day the expression amplitudes of negative regulators *CCA1* and *LHY* are epigenetically down-regulated, whereas positive regulators *TOC1* and *GI* are epigenetically upregulated in the *Arabidopsis* allopolyploids and hybrids [37]. The repression of negative circadian clock regulators is directly related to the upregulation of downstream genes in chlorophyll biosynthesis and starch metabolism. The role of circadian clock regulation for physiological and metabolic fitness is highly conserved among plant and animal kingdom [38,39]. In plants, *CCA1*, *LHY*, *TOC1* and circadian clock-associated pseudo-response regulators are highly conserved between *Arabidopsis* and rice, and many of these regulators display the same diurnal expression patterns in rice as in *Arabidopsis* [40]. This molecular clock model may suggest a general mechanism for increased growth vigor in hybrids and allopolyploids [37].

Genomic stress and nonadditive gene expression in allopolyploids

Phytohormone and stress responsive genes tend to be nonadditively expressed in *Arabidopsis* allopolyploids [28]. Many genes involved in the ethylene biosynthesis pathway are repressed in one or two allotetraploids, which may induce changes in a wide range of developmental processes and fitness responses. In addition, 31 of 33 nonadditively expressed heat shock protein (HSP) genes are repressed, consistent with repression of other stress-responsive genes in *Arabidopsis* allotetraploids (Chen, unpublished data). In resynthesized wheat allohexaploids, 6 of 8 putative HSPs were repressed [31]. Genome-wide analysis of genomic and gene expression data indicate that stress-related genes are preferentially retained during polyploidization [41] and show higher levels of expression divergence in *A. thaliana* and in resynthesized and natural allotetraploids [42]. Repression of HSPs and stress-related genes in allopolyploids suggests that genome merger and/or doubling suppresses defensive pathways, which may promote growth vigor in response to “genomic shock” stress in interspecific hybrids [43]. HSP90 is known to be a capacitor for modulating genetic variation

in plants and animals [44]. It is conceivable that many stress-responsive genes are temporally down-regulated in the allopolyploids in order to promote growth vigor or these genes may confer enhanced resistance and/or selective advantage under stress conditions.

Tissue-specific expression and a developmental role of nonadditive gene expression in allopolyploids

Nonadditive expression of homoeologous rRNA loci is developmentally regulated [27]. Silenced rRNAs genes in the leaves are reactivated in flower organs including petals, sepals, anthers and pollen during flower development, which is consistent with different sets of the genes that are nonadditively expressed in leaves or flowers [28]. Adam et al. [45] found that 10 of 40 genes examined display tissue- or organ-specific expression of the homoeologous loci. Recent estimates using homoeolog-specific microarrays indicate that ~40% of 60 homoeologs examined show biased expression in at least one of 24 cotton tissues examined [32], although some allelic expression patterns vary using different methods. This amazingly high level of tissue-specific expression of homoeologous loci suggests a general role for developmental regulation in nonadditive gene expression in allopolyploids.

A stochastic and locus-specific feature of nonadditive gene expression in allopolyploids

Nonadditive expression can be established rapidly or within several generations following polyploidy formation [19]. Among stochastically expressed genes, there is a trend toward the expression patterns that are fixed in stable or natural allopolyploids. In *Senecio* allopolyploids, the majority of differentially expressed genes in resynthesized and natural *S. cambrensis* are similar [30]. In *Arabidopsis*, many nonadditively expressed genes are common in two independently resynthesized allotetraploids [28]. A mechanism for rapid and stochastic establishment of nonadditive gene expression in allopolyploids may lead to natural variation for adaptive selection and domestication. Homoeologous genes can provide extra settings of gene control in response to changes in environmental cues and developmental programs, as superior gene expression patterns may be selected. Indeed, nonadditive regulation of multiple copies of *FRI* and *FLC* mediates flowering time variation and adaptation in *Arabidopsis* allopolyploids [46].

Expression changes in the homoeologous loci may be independent of chromosomal locations [47] or coordinated within a chromosomal segment [48], suggesting a complexity of chromatin-mediated gene expression changes in allopolyploids.

Small RNAs and nonadditive gene expression in interspecific hybrids and allopolyploids

Small RNAs, including microRNAs (miRNAs), small interfering RNAs (siRNAs), and *trans*-acting siRNAs (tasiRNAs), mediate post-transcriptional regulation, RNA-directed DNA methylation, and chromatin remodeling [49]. Recently, Ha et al. [50] found roles for small RNAs in maintaining genome, chromatin stability and modulating nonadditive gene expression in *Arabidopsis* allopolyploids (Figure 1). Repeat-associated siRNAs (rasiRNAs) diverged rapidly, and <20% of rasiRNAs are shared between *A. thaliana* and *A. arenosa*. Some rasiRNAs are associated with gene repression in *A. thaliana* but weakly with gene expression changes in allotetraploids. Interestingly, ~5.5% of 6,000 siRNA-generating transposons in *A. thaliana* lost siRNAs in F₁, which may be a consequence of genomic shock and genome instability [43]. In stable allopolyploids, the siRNAs are restored. Loss of paternal siRNAs has also been documented during the development of ovules and seeds [51] and pollen [52].

Unlike siRNAs, many miRNA and tasiRNA loci are conserved in sequences and commonly identified in both the allotetraploids and progenitors. Growth and developmental variation between the parents may be controlled by miRNAs and their targets. In the allotetraploids and their progenitors, ~50% and ~40% of miRNAs and tasiRNAs studied are differentially

expressed in leaves and flowers, respectively [50]. Like protein-coding genes, there is also a tendency of repressing *A. thaliana* miRNAs, although both *A. thaliana* and *A. arenosa* miRNAs can be repressed in allotetraploids. Nonadditive accumulation of miRNAs is at least partially related to nonadditive expression of miRNA biogenesis genes such as *DCL1* and *AGO1*. Moreover, some miRNAs also accumulate differently between resynthesized and natural allotetraploids, suggesting a role of miRNAs in allopolyploid evolution. The expression levels of miRNAs and targets are inversely correlated in the allotetraploids. Among *A. thaliana* and *A. arenosa* targets, miRNAs preferentially degrade *A. thaliana* targets over *A. arenosa* targets. Moreover, several targets of *A. thaliana* and *A. arenosa* are differentially expressed in the allotetraploids, suggesting the role of target preference for homoeologous transcripts.

Summary and perspectives

After prezygotic barriers are overcome, rapid and dynamic changes in genome structure and gene expression occur in newly formed autopolyploids and allopolyploids (Figure 1). Some changes are rapid and fixed immediately after polyploidization, whereas others are stochastic and gradually established in paleopolyploids and stable allopolyploids. Genome doubling and dosage effects are the primary consequences of autopolyploidy, whereas genome merger has a greater effect than genome doubling on genomic and gene expression changes in allopolyploids. Sequence deletions/insertions and chromosomal rearrangements are observed in some, but not all allopolyploids. This is probably related to the genetic distance between progenitors and/or specific genes that inhibit or promote pairing between homoeologous chromosomes. Much of the functional plasticity in polyploids is correlated with gene expression changes at transcriptional and posttranscriptional levels. Such gene expression changes are controlled largely by epigenetic mechanisms, which are therefore implicated as direct and indirect regulators of physiological and developmental variation in allopolyploids [37,46,47]. Many other changes including nonadditive regulation of stress and phytohormone responsive networks, developmental and tissue-specific expression of homoeologous loci [27,45], stochastic changes in homoeologous gene expression [19], and miRNA expression variation between closely related species and in the allopolyploids [50] also suggest epigenetic causes. Current evidence suggests that plasticity in the regulation of duplicate genes and genomes, much of which originates from epigenetic factors, provides a novel pathway for functional diversification and the evolution of adaptive traits in polyploids.

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Figure 1.

Mechanisms for gene expression changes in polyploids. Allotetraploid formation is usually impaired by the hybridization barrier (red stop sign) between species. An allotetraploid may undergo rapid changes via genetic and epigenetic mechanisms, dosage regulation, and regulatory interactions. First, genetic changes (e.g., chromosomal rearrangements and gene loss) may cause gene expression and phenotypic variation [21]. Some duplicate genes may diverge expression patterns [41] and the half-life of an active duplicate gene that becomes mutated or lost is estimated to be 2-7 million years [4]. Second, regulatory proteins produced from orthologous genes may generate incompatible products (*heterodimers between red squares and blue circles*), leading to silencing of one homoeologous gene. Alternatively, homoeologous proteins may perform better than the homozygous forms, which may explain overdominant effects on hybrid vigor [13]. Third, gene expression patterns may be reprogrammed by epigenetic changes in new allopolyploids. Hybridization or allopolyploidy

induces formation of heterochromatin and euchromatin, resulting in gene silencing or activation via transcriptional and posttranscriptional mechanisms. Finally, dosage regulation suggests additive effects of gene expression in polyploids, leading to increased levels of expression and phenotypic variation. The dosage may augment the effects of hybridity (or genome merger) on gene expression and phenotypes. It is notable that these mechanisms are not mutually exclusive [13]. Gene expression changes may be selected by natural and/or artificial forces that facilitate adaptation and development.