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Review

The Evolutionary Consequences of Polyploidy

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Polyploidization, the addition of a complete set of chromosomes to the genome, represents one of the most dramatic mutations known to occur. Nevertheless, polyploidy is well tolerated in many groups of eukaryotes. Indeed, the majority of flowering plants and vertebrates have descended from polyploid ancestors. This Review examines the short-term effects of polyploidization on cell size, body size, genomic stability, and gene expression and the long-term effects on rates of evolution.

One of the most striking features of genome structure is its lability. From small-scale rearrangements to large-scale changes in size, genome comparisons among species reveal that variation is commonplace. Even over the short time course of laboratory experiments, chromosomal rearrangements, duplications/deletions of chromosome segments, and shifts in ploidy have been observed and have contributed to adaptation (Dunham et al., 2002; Gerstein et al., 2006; Riehle et al., 2001). Changes in genome structure typically have immediate effects on the phenotype and fitness of an individual. Beyond these immediate effects, changes in genome structure might allow evolutionary transitions that were previously impossible. For example, by introducing an additional complement of chromosomes, polyploidization might release gene duplicates from the constraints of having to perform all of the functions of a gene (pleiotropy), providing extra "degrees of freedom" upon which selection can act to favor new functions. Polyploidization can also stimulate further structural changes in the genome, providing polyploid lineages with genomic variation not available to diploid organisms. Indeed, it has been proposed that tetraploidy may be an intermediate stage in some cancers, facilitating a cascade of structural changes that disrupt normal controls to cell growth (Storchova and Pellman, 2004). Here, I discuss the evolutionary impact of polyploidization, beginning with the prevalence of polyploidy, and then I explore the longer-term consequences of polyploidy on the rate and nature of evolutionary transitions.

Incidence of Polyploidization

Polyploidization is the increase in genome size caused by the inheritance of an additional set (or sets) of chromosomes (Figure 1). The duplicated sets of chromosomes may originate from the same or a closely related individual ("autopolyploid") or from the hybridization of two different species ("allopolyploidy"). When polyploidization involves duplicated sets of chromosomes that share homology but are sufficiently distinct due to their separate origins, these pairs of chromosomes are referred to as homeologs (see Figure 1). Polyploidy is especially prevalent among hybrid taxa, an association thought to be driven by problems with meiotic pairing in diploid hybrids, which are solved if each homeologous chromosome has its own pairing partner. Additionally, diploid hybrids form unreduced gametes (which have the same number of chromosomes as somatic cells) at unusually high rates (Ramsey and Schemske, 2002), increasing the rate of formation of polyploids from hybrid lineages. By combining traits from two parental species and ensuring fair segregation of these traits, allopolyploids potentially benefit from "hybrid vigor" (where hybrids have characteristics that make them superior to both parental species) and an altered ecological niche without the problems associated with segregation and breakdown at the F_2 generation that occurs among diploid hybrids.

Chromosomes that have previously diverged and been brought together by hybridization typically segregate as bivalents (Figure 1C; Ramsey and Schemske, 2002). Genomic analyses have begun to unravel the genes responsible for bivalent pairing, ensuring that homologs rather than homeologs pair during meiosis (e.g., at the *Ph1* locus in polyploid wheat; Griffiths et al., 2006). In contrast, autopolyploids more often exhibit multivalent pairing than allopolyploids (Figure 1B), ~3.5 times more so in plants (Ramsey and Schemske, 2002). In most cases, descendants of a polyploidization event in the distant past ("paleopolyploids") exhibit bivalent pairing of chromosomes and disomic inheritance (as if diploid). This observation has traditionally led to the conclusion that autopolyploids are ephemeral whereas allopolyploids give rise to the majority of long-lasting lineages (Grant, 1971; Stebbins, 1950). Bivalent pairing, however, can occur and is even more prevalent (63.7%) than multivalent pairing (28.8%) among newly formed autotetraploid plants (Ramsey and Schemske, 2002). Although bivalent pairing is initially nonpreferential in autopo-

lyploids, leading to tetrasomic inheritance (Figure 1), segregating polymorphisms, especially rearrangements and indels (insertions and deletions), may increase pairing fidelity over time ultimately yielding disomic inheritance. Increased pairing fidelity may also stem from genetic changes, such as at the *Ph1* locus in wheat (Griffiths et al., 2006). Thus, one cannot assume that a paleopolyploid is necessarily allopolyploid solely because it exhibits disomic inheritance; additional evidence is needed, such as phylogenetic evidence that different genomic regions are more closely related to different parental species. Autopolyploids are also less frequently recognized as distinct species than allopolyploids, even when they are reproductively isolated and morphologically differentiated from their diploid parents (Soltis et al., 2007). Thus, recent papers have argued that autopolyploidy may contribute more to evolution and species diversification than traditionally thought (Soltis et al., 2007).

Mutations affecting ploidy occur relatively frequently in both plants and animals. Plants produce unreduced gametes, a common route to polyploidization, at an average rate of ~0.5% per gamete (Ramsey and Schemske, 1998). Both unreduced gametes and polyspermy contribute to the production of polyploid animals. Among chicken embryos, 0.9% are triploid or tetraploid (Bloom, 1972), and among spontaneous human abortions, 5.3% are triploid or tetraploid (Creasy et al., 1976). Placing these rates in context, gene duplication events are much rarer, with a roughly 10^{-8} chance of occurring per gene copy per generation (Lynch, 2007). Conversely, aneuploidy, the gain or loss of a single copy of a chromosome, can be much more frequent; for example, aneuploids were four times more common than polyploids among the aborted fetuses examined by Creasy et al. (1976).

The evolutionary contribution of structural alterations to the genome depends on their ability to persist. Although the probability of a gene duplication is low, the half-life of gene duplicates is very long (over a million generations; Lynch, 2007). Conversely, aneuploids often have low fitness and, in mammals, rarely survive to reproduce. Indeed, it is exceedingly rare for a homologous chromosome pair to be lost or duplicated among all members of a population. In mammals and birds, ploidy changes are also typically fatal, with polyploids dying early during development. Interestingly, polyploidy is lethal regardless of the sexual phenotype of the embryo (e.g., triploid XXX humans, which develop as females, die, as do triploid ZZZ chickens, which develop as males), and polyploidy causes much more severe defects than trisomy involving the sex chromosomes (diploids with an extra X or Y chromosome). Thus, in mammals and birds, evidence suggests that a general disruption of development—not problems restricted to sex determination—is the root cause of the failure of polyploids to persist. Specific developmental problems in human polyploid aborted fetuses have been attributed to abnormal imprinting and placental development (see references in Otto and Whitton, 2000).

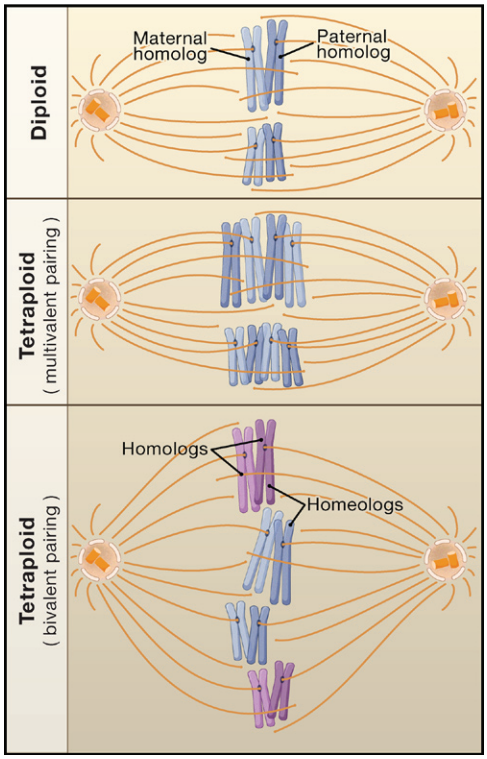

Figure 1. Polyploidy Terminology

Two nonhomologous chromosomes are shown (long and short), with each X-shaped chromosome representing a pair of sister chromatids joined at the centromere. In diploids (A), each chromosome consists of a homologous pair, with one chromosome inherited from the mother and one from the father. In tetraploids (B and C), the chromosomes are further doubled. When the duplicated chromosomes are very similar to one another, they might align randomly in pairs during meiosis (bivalent pairing; not shown) or all align together (multivalent pairing; B). In either case, gametes may inherit any combination of parental chromosomes (multisomic inheritance), and mutations that arise on one chromosome can spread to all other copies, inhibiting their divergence. When polyploidization involves chromosomes that are sufficiently distinct (that is, "homeologs"; differentiated by blue and purple), the more similar pair of chromosomes tend to align together to the exclusion of the other pair (C). With strict bivalent pairing, the homeologs behave as distinct chromosomes and segregate independently (disomic inheritance), allowing their divergence. Newly formed autopolyploids typically exhibit multisomic inheritance, whereas newly formed allopolyploids exhibit a variety of patterns of inheritance, depending on the cross (Ramsey and Schemske, 2002).

In many taxa besides mammals and birds, however, polyploidy is surprisingly well tolerated. Polyploid lineages often persist in plants, which is immediately apparent from the excess of even over odd chromosome numbers (Figure 2). Because doubling a number always generates an even number, this excess of even chromosome numbers is a predictable consequence of polyploidization. By contrast, the fusion or fission of chromosomes simply switches whether a cell has an even or odd number of chromosomes. The excess of even chromosome numbers can be used to infer how often changes in chromosome number are due to polyploidization (42% of the time in ferns, 32% in monocots, and 18% in dicots;

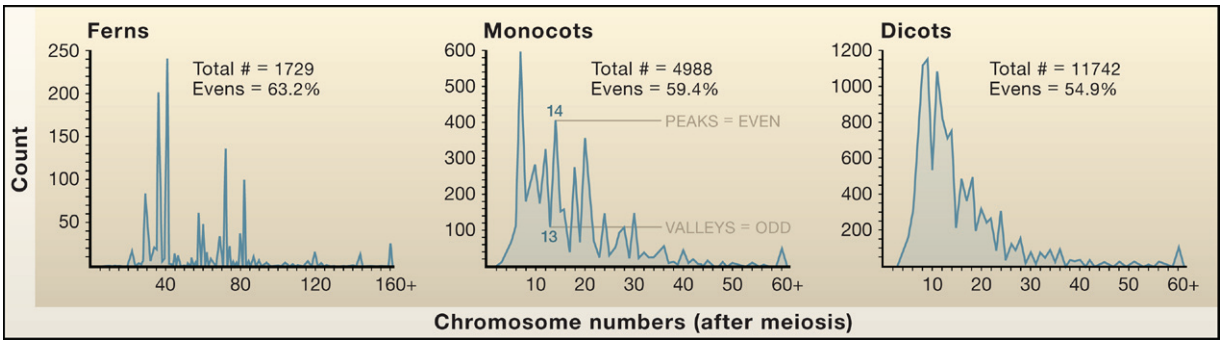

Figure 2. Widespread Polyploidization in Plants

The saw-toothed pattern in the distribution of chromosome numbers provides evidence for widespread polyploidization in plants. Because doubling a number always generates an even number, an excess of even numbers of chromosomes is a predictable consequence of polyploidization. The percentage of plant species with even numbers of chromosomes is greater than expected and can be used to infer how often changes in chromosome number are due to polyploidization. In each case, the proportion of even-numbered chromosomes is significantly different from 50% (binomial test $p < 0.0001$; Otto and Whitton, 2000). Fern data from Löve et al. (1977). Angiosperm data from Grant (1971).

Otto and Whitton, 2000). In various plant genera, the rate at which polyploids arise and persist is on the order of 0.01 per lineage per million years, roughly 1/10th the rate of speciation (Meyers and Levin, 2006). With such a high rate of polyploidization per speciation, we would expect a large fraction of plant species to have undergone polyploidization at some point in their evolutionary past. Previous studies had suggested that polyploidy occurred sometime in the past of 57% (Grant, 1963) to 70% (Goldblatt, 1980; Masterson, 1994) of flowering plants, based solely on chromosome numbers among extant species. Recent genomic analyses indicate that an early polyploidization event may predate the radiation of flowering plants (Bowers et al., 2003), suggesting that 100% of angiosperms are paleopolyploid. Unfortunately, evidence for such ancient polyploidization events is almost always tentative because of the loss of sequence homology and synteny over evolutionary time. Although polyploidization is less prevalent in animals, nearly 200 independent examples of polyploidy have been reported in insects and vertebrates (Table 1), with many more cases known among other invertebrate groups (Gregory and Mable, 2005).

If polyploidy were an evolutionary dead end, we would expect polyploid taxa to be near the tips of the tree of life and to be relatively species poor. Instead, several polyploidization events are ancient, and several of these events gave rise to species-rich groups. For example, multiple independent polyploidization events occurred early in the evolution of plants (Freeling and Thomas, 2006), fish (the diverse group of ray-finned fishes, Catostomidae, Salmonidae, and different groups of Cyprinidae), and amphibia (Syrinidae), with evidence for two additional rounds of genome duplication at the base of the vertebrate tree of life (Dehal and Boore, 2005), as proposed by Ohno (1970; see Otto and Whitton, 2000 for additional examples). This data is sufficient to conclude that polyploidy is not an evolutionary dead end, but it does not prove that polyploidization contributes to evolutionary success. Whether polyploidization increases the longevity and species richness of a group relative to taxa that have not undergone polyploidization is a question that has yet to be answered.

Why is it that the duplication of a whole genome often gives rise to lineages that persist over evolutionary time whereas the duplication of a single chromosome virtually never does? One plausible explanation is that polyploidization preserves the balance of gene products (Guo et al., 1996; Papp et al., 2003). This "balance hypothesis" is an old idea that traces back to the pre-genomics era; for instance, Haldane (1932) pointed out that morphological changes were more marked in trisomic than in triploid plants, arguing that "In the latter case the number of genes of all sorts is increased equally, in the former the balance is upset" (p. 29 in Haldane, 1990). Consistent with the balance hypothesis, genes duplicated by

Table 1. Polyploidization in Insects and Vertebrates

Reproduction	Insects	Fish	Amphibia	Reptiles	Birds	Mammals	Total
Parthenogenesis	89	9	3	15	0	0	106
Sexual	2	23	26	1	0	1[a]	54
?	0	18	1	0	0	0	19

A summary of data on the number of polyploidzation events. (Data derived from Otto and Whitton, 2000, online Table 1; and Gregory and Mable, 2005, Table 1). Mode of reproduction of the polyploid is specified, where known.

[a]The only reported case of polyploidization in mammals involves the related red and golden viscacha rats (Gallardo et al., 2004).

polyploidization persist longer, on average, than genes duplicated individually (Lynch, 2007). Another explanation is that organisms have evolved mechanisms to cope with changes in ploidy because of the natural variation in genome copy number associated with mitotic and meiotic cell cycles (as DNA replicates and cells divide). According to this "evolved-robustness hypothesis," organisms with a regular alternation of generations, with mitoses in both haploid and diploid phases, are predicted to be especially tolerant of shifts in ploidy. In addition, somatic variation in ploidy ("endopolyploidy") is a normal part of development in many animals as well as plants (Gregory, 2005). Most famously, the chromosomes of the salivary gland are highly replicated in flies, leading to visible polytene chromosomes. In mammals, multinucleate cells are found in hepatocytes and osteoclasts, whereas megakaryocytes, trophoblasts, and hepatocytes display endopolyploidy (that is, have a nucleus with multiple copies of the normal complement of DNA). In summary, the existence of regular mitotic cell cycles, an alternation of generations, as well as endopolyploidy ensures that organisms have experienced, and survived, an evolutionary history at different ploidy levels. The balance hypothesis and the evolved-robustness hypothesis are not opposing explanations. Instead, they may serve as proximate and ultimate explanations for the same phenomenon—present-day organisms function better with a balanced set of chromosomes because their evolutionary past involved changes in ploidy that preserved the balance, but not the absolute number, of chromosomes.

Immediate Effects of Polyploidization

At a phenotypic level, the effects of polyploidization are often mild and idiosyncratic. Cell volume generally rises with increasing genome size (Cavalier-Smith, 1978; Gregory, 2001), although the exact relationship between ploidy and cell volume varies among environments and taxa. In yeast, for example, the volume of diploid cells in rich media is 2.4 times that of haploid cells at 30°C but only 1.1 times at 37°C (Mable, 2001). Larger cells tend to have smaller surface area to volume ratios, a phenomenon thought to lower the growth rate of polyploid cells. Whether or not cell geometry affects growth rate depends on the environment (Adams and Hansche, 1974; Mable, 2001), as expected given that transport across the membrane limits growth only under certain circumstances (Weiss et al., 1975). Perhaps as a consequence of a slower metabolism, polyploids tend to exhibit slower development (Levin, 1983), but this pattern is not universally true and can be reversed (e.g., in groups where polyploid eggs or seeds are larger). Interestingly, not all features of a cell scale with ploidy level, which can have important side consequences. For example, Storchova et al. (2006) showed that kinetochore size and length of the pre-anaphase spindle do not scale with ploidy level, whereas the spindle pole body does. These authors argue that changes in ploidy thus upset geometric relationships among key components of the machinery used to segregate chromosomes during meiosis, potentially explaining the higher rate of chromosome nondisjunction in tetraploids. To prevent the detrimental effects of genomic instability, animals may have evolved mechanisms limiting the proliferation of tetraploid cells (see Essay by N.J. Ganem and D. Pellman on page 437 of this issue), which would present another barrier to the establishment of polyploid lineages.

Although cell size typically is larger in polyploids, adult size may or may not be altered; as a rough generalization, polyploidization is more likely to increase adult body size in plants and invertebrates than in vertebrates (Gregory and Mable, 2005; Otto and Whitton, 2000). The poor correlation between cell size and organismal size was even remarked upon by Albert Einstein, who wrote "Most peculiar for me is the fact that in spite of the enlarged single cell the size of the animal is not correspondingly increased" (Fankhauser, 1972). The key to accurately predicting the effects of ploidy on body size must come from developmental biology. In cases where morphogen gradients guide development, ploidy need not affect adult body size (Day and Lawrence, 2000) because ploidy need not alter the overall density of cellular material, only how it is packaged (i.e., into cells that are twice as large and carry twice as much DNA). By contrast, where growth is determined by cell-cell interactions or where there is a fixed number of cells in the adult, ploidy, by altering cell size, should directly influence adult size (Gregory et al., 2000).

A surprising feature of many newly formed polyploids is that their genomes are unstable and undergo rapid repatterning (Wendel, 2000). For example, Song et al. (1995) observed extensive genomic rearrangements and fragment loss within five generations in newly created polyploid *Brassica* hybrids, and more recent studies have documented genomic changes soon after formation of wheat and *Arabidopsis* allopolyploids (but not in cotton or *Spartina*; Chen and Ni, 2006). In most examples studied to date, rapid genomic repatterning has been observed in allopolyploids, and there are many reasons to expect that hybridization may be causally responsible. Transposable elements that are repressed within each parent lineage but activated in hybrids can facilitate the movement of genes and promote unequal crossing over. For example, Josefsson et al. (2006) found that maternally derived siRNAs are not sufficient to repress retrotransposons in the paternal genome of *Arabidopsis thaliana* × *A. arenosa* hybrids. Divergence of centromeres and centromeric histones can lead to segregation distortion and nondisjunction in hybrids (Malik and Bayes, 2006). In addition, nonhomologous recombination and nonreciprocal exchanges are particularly likely among homeologous chromosomes that bear structural rearrangements. Nevertheless, genomic repatterning in polyploids is not entirely driven by hybridization. In autotetraploids of both *Candida albicans* (Bennett et al., 2003) and *S. cerevisiae* (Gerstein et al., 2006), reduc-

tion in genome size through chromosome loss has been observed, largely restoring the diploid complement. The exact mechanism by which this reduction occurs is unknown, but similar reductive divisions (termed "neosis") have been observed in human cell lines that have undergone endopolyploidization in response to carcinogens (Rajaraman et al., 2005).

By altering the genomic context of genes, genomic repatterning can increase the genetic variability available to newly formed polyploid populations. This variability might be especially important given the bottleneck in population size associated with the founding of new polyploid lineages. That said, genetic variability can only fuel the evolution of a polyploid population if individuals can survive the onslaught of genomic mutations. If the genomic mutation rate is too high and the fitness effects of mutations too severe, extinction is the likely outcome. Polyploid lineages that have survived are almost certainly a biased subset of those that have been generated; we only witness those lineages that chanced upon a particularly fit and stable genomic configuration soon after polyploidization.

In addition to structural changes, polyploids often exhibit changes in gene expression (Liu et al., 1998; see reviews by Chen and Ni, 2006 and Adams and Wendel, 2005). This is especially true of allopolyploids, which exhibit changes in methylation (e.g., 30% of the methylation patterns were altered in allopolyploids of *Spartina*; Salmon et al., 2005), disruption of heterochromatin (potentially explaining activation of the retrotransposon *ATHILA* in *Arabidopis thaliana* × *A. arenosa* allopolyploids; Josefsson et al., 2006), alterations in imprinting (Josefsson et al., 2006), and biased expression of homeologs (e.g., 43% of genes exhibited biased expression in allopolyploid cotton; Udall et al., 2006). These changes in gene expression are strikingly idiosyncratic and tissue specific. For example, among newly formed cotton allopolyploids, Adams et al. (2003) found that alleles from the two hybridized genomes (designated A and D) differ in expression patterns among the tissues examined for 11 out of the 18 genes considered. In the most extreme case, *adhA* was entirely expressed from the A gene in carpels but from the D gene in petals and stamen. In some cases, it has been shown that the majority of changes in gene expression are due to hybridization, rather than ploidy changes per se (Albertin et al., 2006; Salmon et al., 2005). Even where ploidy matters, disruptions in gene regulation have been associated with divergence between the parental species (e.g., *A. thaliana* contains fewer *ATHILA* elements and these elements differ in sequence from those in *A. arenosa*; Josefsson et al., 2006). Consequently, we would expect much smaller effects on gene expression in autopolyploids. Indeed, microarray analysis has revealed relatively few changes in the relative expression of genes in autotetraploids, for example in maize (Guo et al., 1996) and in yeast (Galitski et al., 1999), and proteomic analysis has similarly revealed few changes (e.g., in cabbage; Albertin et al., 2005).

Although genomic repatterning and gene expression changes are more extensive in studies of allopolyploids, we have only limited information about how the extent of change depends on the genetic distance between the parental genomes. It may be that the changes in expression observed are particularly dramatic when the allopolyploids studied involve very divergent genomes (e.g., 7.5 million years [MY] in the case of the cotton studied by Adams et al., 2003; 11 MY between the *Brassica rapa* and *B. nigra* studied by Song et al., 1995, as estimated by Shavorskaya and Lagercrantz, 2006). Indeed, Song et al. (1995) observed that less extensive genomic rearrangements occurred in the allopolyploid formed from the more closely related *B. rapa* and *B. oleracea* (separated by ~6 MY, based on Figure 1 of Shavorskaya and Lagercrantz, 2006). There remains a need to explore how the extent of genomic repatterning and changes in gene expression depend on the divergence between the parental genomes. It is possible that autopolyploids, if formed from distantly related individuals within a species, might also exhibit rapid genomic repatterning and gene expression changes. Alternatively, dramatic changes might be limited to allopolyploids formed from distantly related lineages.

Establishment of Polyploidy

What allows a polyploid lineage to become established once it has arisen? Although many potential evolutionary advantages and disadvantages of polyploidization have been proposed (reviewed below), they pale in significance relative to the immediate ecological differences between a newly formed polyploid and its diploid relatives. The reason has to do with timing: a polyploid lineage must survive long enough for evolution to act, and it will do so only if it is not immediately outcompeted by its diploid relatives. Like most mutations that affect fitness, polyploidization often reduces fertility and/or survival; Ramsey and Schemske (2002) found, on average, a 20% reduction in pollen viability and a 50% reduction in seed production in their survey of newly formed plant polyploids. However, occasionally, the altered suite of characters displayed by a polyploid—for instance, drought tolerance or pathogen resistance—might better suit the environment or shift a polyploid into a distinct ecological niche (Jackson and Tinsley, 2003; Levin, 1983; Ramsey and Schemske, 2002). As argued by Stebbins (1984), polyploidy can permit ecological traits from two parental species to be combined together and stabilized as fixed heterozygotes (assuming the hybridizing genomes are sufficiently distinct that disomic inheritance occurs; Figure 1). This advantage may partially account for the unusually high proportion of polyploidy plants in previously glaciated regions, where the hybridization of previously isolated populations may be frequent, where new environments are common, and where competition may be limited (Brochmann et al., 2004; Stebbins, 1984).

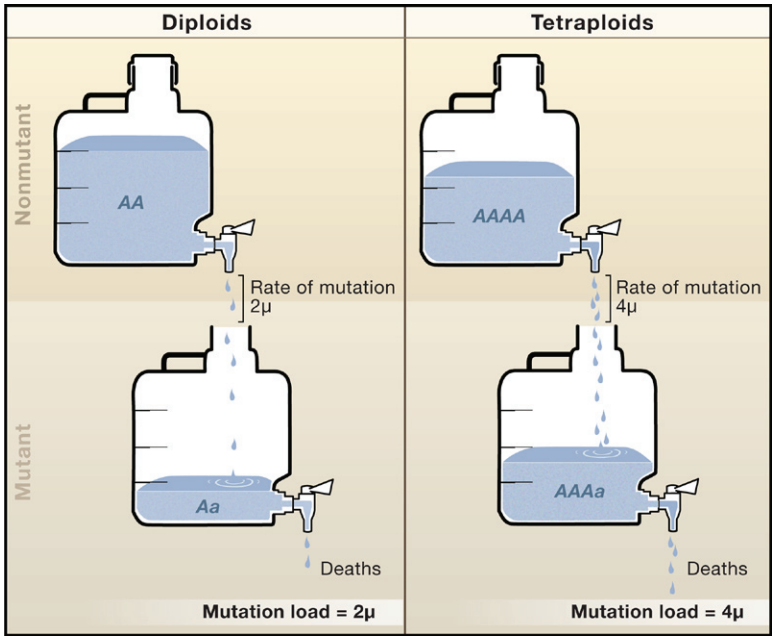

Figure 3. Polyploidization Decreases Mean Fitness at Equilibrium

By doubling the number of gene copies, tetraploids undergo twice as many mutations as diploids. This can be visualized as doubling the flow rate from nonmutant individuals (top tanks) to mutant individuals (bottom tanks). Ultimately, the flow rate out of the mutant class must equal the flow rate into it; this balance of flow rates is accomplished by a higher equilibrium level of mutant individuals in tetraploids (bottom right tank), resulting in twice the number of deaths due to mutation ("mutation load") in tetraploids compared to diploids.

One hurdle to the establishment of polyploids is reproductive: mating between a newly formed tetraploid and a diploid relative produces triploids with low fitness. Triploid seeds often have lower germination rates. Interestingly, germination success often depends on the source of the haploid versus diploid gamete. Data reviewed by Ramsey and Schemske (1998) indicate that triploid seeds are 19.9% as viable as diploid seeds when the ovule is diploid but only 4.8% as viable when the pollen is diploid. It has been argued that these failures result from an imbalance of maternally and paternally imprinted genomes in the endosperm (Haig and Westoby, 1991), a hypothesis that is supported by the effects on seed development observed when imprinted genes are disrupted (e.g., the *MEDEA* mutation in *Arabidopsis*; Grossniklaus et al., 1998). Even if they reach maturity, triploid individuals also have severely reduced fitness in most sexual taxa because of the fertility problems associated with producing aneuploid gametes; on average, pollen fertility of triploids is only 31.9% (Ramsey and Schemske, 1998). Several factors enable polyploid plants to overcome the hurdle posed by triploidy, including the ability to self or asexually reproduce, the ability to persist for long periods of time until a suitable mate is found (perenniality), or the tendency to mate assortatively (e.g., according to body size, flowering time, or habitat). Moreover, both genetic and environmental factors are known to alter the frequency at which polyploids are formed, making it more likely that where there is one new polyploid, others will be found. Finally, even the production of triploids is no longer considered to be the death knell of new polyploid lineages: of the viable gametes produced by triploids, a disproportionately high fraction are euploid (having one or more full sets of chromosomes) and can contribute to the production of polyploid offspring (Henry et al., 2005; Ramsey and Schemske, 1998).

Evolution of Polyploids

It is often thought that polyploids have an advantage over diploids via their greater ability to mask deleterious mutations. It is true that a deleterious mutation is more likely to be masked in individuals with more nonmutant alleles, but this masking only serves to allow the mutation to persist and reach a higher frequency (Figure 3). At equilibrium, the benefits of masking are overwhelmed by the higher frequency of mutant alleles. If mutations occur at rate μ per gene copy and each individual carries c gene copies ($c = 2$ in diploids; $c = 4$ in tetraploids), the equilibrium fitness of a population is reduced by $c\mu$. Thus, eventually, polyploids suffer more from recurrent deleterious mutations than diploids. A newly formed polyploid, however, may gain a transitory benefit by masking mutations, before mutant alleles reach the higher equilibrium frequency expected in a polyploid (Otto and Whitton, 2000). In addition, polyploids tend to suffer less of a fitness reduction upon inbreeding ("inbreeding depression") because they are less likely to form fully homozygous offspring than diploids (Ronfort, 1999). For precancerous cells reproducing mitotically, similar temporary benefits of endopolyploidy arise from masking somatic mutations (akin to Orr, 1994) and from reducing the loss of heterozygosity due to mitotic recombination (which, like inbreeding, exposes deleterious recessive alleles to selection). However, these benefits will be offset if polyploid cells are less stable genetically and prone to mutation (Storchova et al., 2006). In short, masking deleterious mutations and ameliorating inbreeding depression should, in theory, provide immediate advantages that can help newly formed polyploid lineages become established, but these advantages diminish over time due to the accumulation of mutations.

Once established, the long-term fate of a polyploid lineage depends on its ability to adapt. One benefit of a higher ploidy level is that it increases the number of gene copies that can harbor a new beneficial mutation. On the other hand, as Stebbins (1971) argued, polyploidy "dilutes the effects of new mutations" because of masking by nonmutant alleles. Consider the rate at which fit-

ness rises due to the accumulation of beneficial alleles at a single gene. Fitness will increase at a rate equal to the rate at which beneficial mutations appear within a population, $\nu\ c\ N$ (where ν is the beneficial mutation rate per gene copy, c is the number of gene copies per individual, and N is the population size) times the chance that a newly arisen mutation survives stochastic loss, P, times the proportional increase in fitness once the mutation is fixed, s (if the beneficial mutation causes a fitness change from W_{old} to W_{new}, $s = (W_{new} - W_{old})/W_{old}$). The probability, P, that a beneficial mutation establishes is approximately $2\ h_c\ s$ (Haldane, 1927), where $h_c\ s$ is the selective benefit of the mutation discounted by the dominance of the mutation when in a single copy, h_c. Altogether, the mean fitness of a population is expected to rise at a rate equal to $\Delta W_c = (\nu cN)(2h_c s)s$ (assuming sexual reproduction and multisomic inheritance, see Otto and Whitton, 2000 for other cases). Thus, all else being equal, tetraploid populations ($c = 4$) should evolve faster than diploid populations ($c = 2$) as long as $h_4 > h_2/2$. This requirement can be satisfied if beneficial alleles are partially dominant over wild-type alleles, but not if they are partially recessive. This back-of-the-envelope calculation emphasizes the key insight that populations at a higher ploidy level may adapt faster or slower than populations at a lower ploidy level, depending on the degree to which mutant alleles are masked.

In asexual populations, including precancerous polyploid cells, there is an additional complication that arises because beneficial mutations that occur in different cells cannot be combined together by sex and recombination. Thus, only beneficial mutations that arise in already fit cell lineages are likely to survive. Theory tailored to asexuals (Orr and Otto, 1994; Otto and Whitton, 2000) indicates that the population size must be sufficiently small and beneficial mutations must be partially dominant for higher ploidy organisms to evolve faster than lower ploidy organisms. In very large populations, beneficial mutations arise often, regardless of ploidy, and their spread is slowed in polyploids due to masking, so that the fastest rate of adaptation should occur in haploids. In small populations, beneficial mutations arise rarely, but they are more likely to arise in polyploids; as long as the fitness advantage of a mutation is not too masked (i.e., as long as dominance is high enough), the fastest rate of adaptation should occur at higher ploidy levels. Two key predictions of this theory have been confirmed experimentally in the budding yeast *Saccharomyces cerevisiae*. Relative to haploid cells, diploid cells evolve more rapidly when population size is decreased (Zeyl et al., 2003) and when response to selection requires dominant mutations rather than recessive mutations (Anderson et al., 2003, 2004). This theory also suggests that, relative to diploid cells, precancerous polyploid cells (whose population sizes are small, at least initially) are more likely to accumulate mutations, especially partially dominant mutations that increase cell growth, predicting a positive association between ploidy level and dominance level of mutations that accumulate in key oncogenes.

The above discussion assumes that "all else is equal," which arguably never holds. Following a change in ploidy, mutation rates per gene may be altered (Mayer et al., 1992). Polyploids may also exhibit higher rates of segregation errors, especially when centrosomes are duplicated, causing an aneuploid cascade, which has been shown to facilitate tumorigenesis (Fujiwara et al., 2005; Storchova and Pellman, 2004).

In addition, selective forces experienced by polyploids may be altered relative to their diploid progenitors. As mentioned above, gene expression can differ between homeologs, even among newly formed allopolyploids, with relative expression varying from tissue to tissue (Adams et al., 2003). Thus, even from the beginning, polyploids need not be simply doubled diploids. Whenever tissue-specific (or stage-specific) patterns of gene expression are altered, duplicated genes face different selective pressures, with each gene copy being selected to improve function when and where it is expressed. Tissue- or stage-specific expression patterns can also arise via mutations that knock out different subfunctions of a gene (Force et al., 1999; Lynch and Force, 2000). Either through immediate specialization or mutational subfunctionalization, the end result is that the fitness landscape faced by a polyploid is different than that faced by the diploids from which it arose, with selection acting to fine tune one or both gene copies for more specialized functions.

Maintenance of Duplicated Genes

Genomic analyses of paleopolyploids have revealed that duplicated genes can persist for millions of years, allowing a long-term contribution of these gene pairs to the evolution of a lineage. For example, ~8% of duplicated genes have remained in yeast over ~100 MY following polyploidization (Seoighe and Wolfe, 1999), ~72% in maize over ~11 MY (Ahn and Tanksley, 1993; Gaut and Doebley, 1997), ~77% in *Xenopus* over ~30 MY (Hughes and Hughes, 1993), ~70% in salmonids over 25–100 MY (Bailey et al., 1978), ~47% in catastomids over ~50 MY (Ferris and Whitt, 1979), and ~33% in vertebrates over ~500 MY (Nadeau and Sankoff, 1997).

If duplicated genes were free to accumulate mutations (that is, if their integrity were not actively maintained by selection), it is very likely that a mutation that eliminates function would accumulate in one of the copies before a beneficial mutation arises that differentiates, and preserves, the gene duplication. Modeling this process, Walsh (1995) showed that inactivation was more likely than the evolution of a novel function ("neofunctionalization"), unless both the population size and proportion of beneficial mutations were high. For example, inactivation is 25 times more likely than neofunctionalization if mutations eliminating function occur 1000 times more frequently than beneficial mutations, assuming that beneficial alleles increase fitness by 0.1% and that the population size is 10000.

Why then are so many duplicated genes preserved when the inactivation of one copy is so likely? Either immediate specialization (Adams et al., 2003) and/or subfunctionalization (Force et al., 1999; Lynch and Force, 2000) of gene expression can prevent duplicated genes from accumulating mutations that eliminate function because the function of each gene copy is necessary at some time or place within the organism. Other mechanisms that preserve newly duplicated genes include the requirement for gene balance, heterozygote advantage, and selection for higher levels of gene expression (see references in Otto and Yong, 2002 and Kondrashov et al., 2002). A new hypothesis has argued that duplicated genes can, if crossregulated, serve to filter out environmental noise and to buffer the end product of transcriptional networks (e.g., the duplicate genes *Hxt1* and *Hxt2* buffer glucose concentrations in yeast by inducing the "back-up" copy in response to a drop in glucose levels), which would account for the maintenance of functionally redundant gene copies (Kafri et al., 2006). Analyses of the rate of silent and replacement substitutions among recently duplicated genes confirm that selection generally preserves both gene copies (Hughes, 1994; Kondrashov et al., 2002), but not necessarily for every one of the original functions of the gene (He and Zhang, 2005). That selection acts to preserve newly copied genes is perhaps not too surprising; mutations eliminating function typically exhibit some reduction in fitness in heterozygous diploids (one mutant: one wild-type allele; Szafraniec et al., 2003), so why would they be entirely neutral at duplicated loci (one mutant: three wild-type alleles)? In fact, experiments with the mutagen ethyl methyl sulfonate (EMS) have indicated that mutations do cause a substantial reduction in fitness in heterozygous tetraploids (Mable and Otto, 2001). Because EMS might have had unintended effects (including direct toxicity) and because rapid evolution of EMS-treated populations biases fitness estimates, more direct fitness assays of polyploids bearing mutations are needed (as in Szafraniec et al., 2003).

The Long-Term Evolutionary "Success" of Polyploids

Although the relative importance of the various processes preserving gene duplicates is under debate, everybody agrees that duplicated genes—whether produced by polyploidization or by single gene duplication—take on a variety of new functions over the long term. Humans have a three-color visual system because of gene duplication (Tan and Li, 1999). Our immune systems are based on highly duplicated gene families (including the major histocompatibility complex and immunoglobulin gene family; Nei et al., 1997), as are the antigenic repertoires of many of our parasites (e.g., Donelson, 1995; Svard et al., 1998). At a broader scale, duplicated gene pairs in yeast are involved in almost twice as many protein-protein interactions as singletons (He and Zhang, 2005). Consequently, the simultaneous input of an entire genome of duplicated genes following polyploidization is thought to be a major facilitator of evolutionary change (e.g., Freeling and Thomas, 2006).

Is there, then, strong evidence that evolution has been facilitated by polyploidization? This is a vexingly hard question to answer. It is not sufficient to point to a particular set of duplicated genes, such as the four HOX clusters that arose at the base of the vertebrate tree of life, as proof that the morphological shifts observed in vertebrates could not have happened without polyploidization. Facing the same selective pressures but without polyploidized genomes, our ancestors may well have undergone similar evolutionary transitions via other means (evolution of regulatory elements, alternative splicing, tandem duplications, etc.). The morphological diversity observed in flies (diptera) and beetles (coleoptera) is tremendous, despite the lack of duplicated HOX clusters (Beeman, 1987; Devenport et al., 2000; Powers et al., 2000), and there is no evidence for a difference in the rate of species diversification between invertebrates and vertebrates (McPeek and Brown, 2007), despite two rounds of genome duplication early in the evolution of vertebrates.

Given the large amount of speculation on the role of polyploidy in evolutionary diversification, there are remarkably few quantitative analyses. Surveying 200 genera of dicots, we found a weak but positive relationship between the percentage of polyploid species (defined as in Stebbins, 1938) and the total number of species (Otto and Whitton, 2000). A similar pattern was found in the flora of the Pyrenees (Petit and Thompson, 1999). Yet these correlative studies are inadequate because larger genera are expected to be older and to have had time to undergo more polyploidization (Meyers and Levin, 2006; Otto and Whitton, 2000). To date, only one study has examined the relationship between polyploidy and species diversity in a manner that corrects for the age and phylogenetic relationships of a group (Vamosi and Dickinson, 2006). This study found that clades with a greater proportion of polyploids indeed had a greater number of species than clades of equal age with a lower proportion of polyploids. Does this mean that polyploid lineages are evolutionarily more successful (increasing speciation rates and/or decreasing extinction rates)? The authors argued against this explanation because a comparison of groups descended from a single polyploidization event and their sister groups failed to show any difference in the number of species (admittedly, with a small sample size). Instead, the authors favored two alternative explanations. First, the process of polyploidization can itself generate species that are reproductively isolated from their diploid progenitors, increasing the number of species as a by-product of polyploidization but without a subsequent effect on diversification rates. Second, an entirely different trait can result in both increased rates of polyploidization and increased evolutionary "success" (as measured by the number of species) without polyploidy being causally involved.

The study by Vamosi and Dickinson (2006) is a step in the right direction, suggesting polyploidy is simply a common mutation, which occasionally spawns ecologically distinct lineages that are able to persist. But more phylogenetic analyses are sorely needed to assess the long-term consequences of polyploidization in a statistically rigorous manner, involving a large number of independent polyploidization events. At present, we lack evidence that polyploidy has altered the rate of evolutionary diversification by promoting speciation or preventing extinction in lineages descended from a polyploidization event. Similarly, we lack evidence that polyploidy has increased the rate of morphological diversification by providing greater genetic flexibility, by releasing constraints due to pleiotropy, or by facilitating genomic restructuring. There are, however, plenty of reasons to believe that changes in ploidy should alter evolutionary processes, including theoretical studies of the rate of adaptation (Orr and Otto, 1994; Otto and Whitton, 2000), evolutionary experiments (Anderson et al., 2003, 2004; Zeyl et al., 2003), and evidence for altered patterns of genomic and molecular evolution (Adams and Wendel, 2005; Blanc and Wolfe, 2004; Chen and Ni, 2006). These studies demonstrate that under the right conditions (such as when beneficial alleles are dominant to currently wild-type alleles) polyploids can evolve at faster rates. Whether the conditions have been "right" in the evolutionary history of eukaryotes, however, and whether shifts in ploidy have increased the rate of speciation or morphological diversification remain to be demonstrated.

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