

## The evolutionary significance of polyploidy

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**Abstract** | Polyploidy, or the duplication of entire genomes, has been observed in prokaryotic and eukaryotic organisms, and in somatic and germ cells. The consequences of polyploidization are complex and variable, and they differ greatly between systems (clonal or non-clonal) and species, but the process has often been considered to be an evolutionary ‘dead end’. Here, we review the accumulating evidence that correlates polyploidization with environmental change or stress, and that has led to an increased recognition of its short-term adaptive potential. In addition, we discuss how, once polyploidy has been established, the unique retention profile of duplicated genes following whole-genome duplication might explain key longer-term evolutionary transitions and a general increase in biological complexity.

### Polyploidy

The condition in which cells or organisms possess more than two complete sets of chromosomes.

Polyploid organisms have multiple sets of chromosomes (BOX 1) as a result of undergoing whole-genome duplication (WGD), which can be caused, for instance, by abnormal cell division. The study of polyploidy dates back more than 100 years to work by Hugo de Vries and G. Ledyard Stebbins Jr (as reviewed in REF. 1), who showed in plants that polyploidy was widespread and commonplace. Nowadays, polyploidy is generally considered to be a common mode of speciation that has far-reaching consequences for plant evolution and ecology. There are also numerous cases of currently polyploid insects, fishes, amphibians and reptiles, although polyploidy is much rarer in animals than in plants<sup>2,3</sup>.

For a long time, ancient polyploidy events, dating back millions of years, were much less well documented than were more recent events; it was not until the advent of genomic technologies that conclusive evidence of ancient WGD events became available. The first clear indication of an ancient polyploidy, in brewers’ yeast, was published in 1997 (REF. 4), followed in 2000 by the first evidence that the plant model system *Arabidopsis thaliana* had also undergone a WGD during its evolutionary past<sup>5</sup>. In 2005, two rounds of WGD were proposed to have occurred during early vertebrate evolution<sup>6</sup>, supporting predictions made by the Japanese geneticist Susumu Ohno 35 years earlier<sup>7</sup>. A third WGD, shared by all teleosts, is thought to have occurred after fishes diverged from land vertebrates<sup>8</sup>. In recent years, many more remnants of ancient polyploidy events have been discovered, largely owing to the sequencing of entire genomes and transcriptomes, and we now have evidence indicating the occurrence of tens, or even hundreds, of WGD events during the past 500 million years (My) of evolution (FIG. 1).

Interestingly, species that are currently polyploid outnumber ancient WGDs by several orders of magnitude<sup>9,10</sup>. This observation can partly be explained by the topology of a phylogenetic tree; as most ancient lineages have become extinct, there are simply fewer places on the ‘older’ parts of a tree to observe a polyploidy event than there are on the more recent ‘tips’. Furthermore, because polyploidization is an irreversible process<sup>11,12</sup>, polyploid abundance is expected to increase over time; thus, again, a higher incidence of polyploidy is expected towards the tips of the tree than at the base. However, because polyploid species are so prevalent, one would expect to find evidence of substantially more ancient WGDs. The many examples of recurrent polyploidy<sup>13</sup> and the existence of many polyploids of fairly recent origin contrast with the scant evidence of ancient polyploidy events, certainly within the same evolutionary lineage (FIG. 1), and provide an interesting paradox<sup>2,9,14,15</sup>.

The paucity of polyploidy events that ‘survive’ and are established in the long term suggests that polyploidy is usually an evolutionary ‘dead end’ (REFS 10,15,16). However, at specific times in evolution, organisms that underwent and survived WGDs might have had some adaptive advantage and outcompeted their diploid progenitors, such that all descendants bear the trace of the WGD event, whereas all sister taxa died out. Therefore, it has been widely debated whether these WGDs, which in many cases characterize major lineages of organisms — such as vertebrates, fishes, and flowering plants including grasses and orchids — have survived by coincidence and are randomly distributed throughout the evolutionary tree of life, or whether they may have occurred at very specific times during major ecological or environmental changes and/or periods of extinction, for instance<sup>17–19</sup>.

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## Box 1 | Allopolyploidy versus autopolyploidy

Polyploids are traditionally classified as either autopolyploids, which arise within a single species as a result of the doubling of one chromosome set, or allopolyploids, which arise through the merging of the chromosome sets of different species (hybridization) and subsequent doubling. Several different scenarios for the formation of both autopolyploids and allopolyploids have been proposed (as reviewed in REF. 81). Allopolyploidy has long been associated with changes in gene expression and epigenetic remodelling<sup>155,156</sup>, and has generally been expected to result in higher adaptive potential than has autopolyploidy. In a hybridization scenario, homologues originate from species that have already diverged, and thus sequence and functional differences are expected from the start, thereby increasing genetic variation and potentially providing the polyploid with an initial selective advantage. For example, novel allelic combinations brought about by the merging of two different species might be responsible for hybrid vigour or heterosis (that is, the enhancement of traits as a result of mixing the genetic contributions of both parents), leading to the formation of more extreme phenotypes in the hybrid population<sup>24</sup>. Allopolyploids exhibiting heterosis could have been, and could be, important targets for crop domestication<sup>154</sup>. However, genome duplication, as in autopolyploids, can also lead to immediate changes in gene expression, physiology and ecological tolerance<sup>29,34,157</sup>. So, although the effects of both allopolyploidy and autopolyploidy (which are potentially different) have been discussed at length<sup>29</sup>, which and how many genes change their expression remains unclear, and often seems to be species-dependent.

### Speciation

The evolutionary process by which biological populations evolve to become distinct species.

### Recurrent polyploidy

Polyploidy that has occurred multiple times in the same population or evolutionary lineage.

### Neutral processes

Mechanisms that do not immediately lead to specific adaptation.

### Adaptive processes

Evolutionary changes that occur as a consequence of natural selection and that are adaptive to a certain environment. Such changes increase survivorship or reproduction by addressing a specific challenge or opportunity presented by the environment.

### Minority cytotype exclusion

A setting in which one cytotype (for example, diploid) is dominant over the other (for example, tetraploid), such that the less common cytotype has difficulty finding suitable partners to mate with.

### Assortative mating

A mating pattern in which individuals with common traits prefer to mate with one another; for example, polyploids mating with other polyploids, rather than with diploids.

In this Review, we discuss the factors affecting short-term survival and the establishment of polyploidy before going on to address its long-term evolutionary potential. In this latter context, we describe important WGDs that have occurred throughout the past 500 My of evolution; elaborate on neutral processes and adaptive processes that might associate WGD with survival and/or invasiveness; and outline how these processes could be responsible for the increasingly observed pattern of WGDs clustered at so-called decisive moments in evolution. Finally, we briefly discuss the importance of polyploidy and WGD for non-germline and clonal systems such as cancer and prokaryotes. We do not discuss here how remnants of ancient duplication events can be discovered or the many different ways in which gene duplicates can evolve novel gene functions, but instead refer readers to excellent previous publications on these topics<sup>20–23</sup>.

### WGDs and short-term adaptive potential

Polyploidy can have detrimental effects on fertility and fitness owing to genomic instability, mitotic and meiotic abnormalities, and gene expression and epigenetic changes. These harmful effects of WGD have been extensively discussed and reviewed elsewhere<sup>24</sup>. Here, we focus on the adaptive potential of polyploids (FIG. 2) and the reasons why some new polyploids might be able to survive and even thrive in the short term<sup>24–29</sup>.

**Effects on interactions between species.** In order to survive, newly formed polyploids need to overcome minority cytotype exclusion by finding polyploid partners to mate with in an environment where they are usually surrounded by diploids. However, at least in plants, polyploidization is often accompanied by a transition from cross-pollination to self-pollination or from sexual to asexual reproduction<sup>24</sup>. Thus, assortative mating by cytotype could help to overcome minority cytotype exclusion and enhance the short-term survival of polyploids<sup>2</sup>.

However, most explanations of the short-term success of polyploids are centred on the effects of genomic changes and increased genetic variation, which are mediated by changes in gene expression and epigenetic remodelling<sup>30–37</sup>. Increased genetic variation can potentially affect the morphology, physiology and ecology of newly formed polyploids, and these changes could, in turn, affect interspecies interactions<sup>26,33,38</sup>. For instance, divergence in traits that are attractive to pollinators can lead to differentiation in pollinator communities<sup>38</sup>, causing the reproductive isolation of diploids and polyploids even within mixed populations, thereby facilitating polyploid establishment<sup>39</sup>. Indeed, it is known that the colour and scent of flowers can differ between polyploids and diploids<sup>40,41</sup>; the preference of certain pollinators for polyploids on the basis of these traits might help to overcome minority cytotype exclusion and contribute to the reproductive isolation of polyploid lineages, and thus to their speciation and establishment.

Interactions with herbivores might also change after polyploidy. It was recently shown that the neofunctionalization of genes following WGD events in flowering plants of the order Brassicales probably allowed these plants to escape herbivory<sup>42,43</sup>. Although the neofunctionalization of genes needs time to evolve, short-term effects of polyploidy on herbivory that are mediated by changes in secondary metabolism<sup>30,44</sup> could be envisioned. For instance, immediate metabolic changes following transitions to polyploidy were recently demonstrated by comparing the metabolic profiles of natural diploids and artificial colchicine-induced autotetraploids of *A. thaliana*. This comparison revealed important differences in the concentrations of metabolites related to the tricarboxylic acid (TCA) cycle and the  $\gamma$ -aminobutyric acid (GABA) shunt, differences that were reflected in the differential expression of genes related to these processes<sup>44</sup>. The functional roles of TCA and GABA metabolites are diverse, but differences in the concentrations of these metabolites could have important adaptive consequences for the specific ecology of diploids and polyploids. Changes in metabolite profiles and possible consequent biotic interactions might also explain why polyploids show increased resistance to pathogens<sup>45</sup>. That is, some polyploid crops and ornamental plants show increased resistance to fungal pathogens, nematodes and insects, although the opposite has also been observed (as reviewed in REF. 26). Thus, evidence is accumulating that polyploidy-related changes in gene expression and epigenetic remodelling can lead to changes in physiology, metabolism and perhaps morphology, and that these changes affect species interactions.

**Effects on environmental robustness.** Increased genetic variation in polyploids might also lead to increased tolerance to a broader range of ecological and environmental conditions, although this theory remains controversial<sup>2,17,26,46</sup>. For instance, it has repeatedly been proposed that polyploids have a higher stress tolerance (environmental robustness) than do diploids, which is supported by the observation that present-day polyploids often occur at increased frequencies in newly created,

disrupted or harsh environments<sup>27,47,48</sup>. An example is the differential distribution of diploid and tetraploid *Neobatrachus* (frog) species in Australia (FIG. 3). However, most of the evidence that WGDs facilitate or accelerate adaptation — for instance, to new or changing environments — is circumstantial because direct tests are difficult to conduct and are therefore rare. That said, some studies exploring the effects of polyploidy on biotic and abiotic stress do exist. For instance, Chao *et al.*<sup>49</sup> found, in naturally occurring tetraploid *A. thaliana* accessions, that polyploid plants confer increased salt tolerance by regulating leaf potassium levels. Other tetraploid plants, such as rice and citrus, have also been shown to have an increased tolerance to salt and drought stress as a result of polyploidy affecting the expression of genes involved in stress and hormone response pathways<sup>50,51</sup>.

**Effects on species diversification.** Polyploidization seems, at least in plants, to occur at a high frequency, and the latest estimates suggest that up to 25–30% of extant flowering plants are ‘young’ polyploids (by which we mean that they are currently polyploid and have not yet been diploidized)<sup>12,52,53</sup>. Conversely, recent simulations of the formation of polyploids have shown that the likelihood of new allopolyploids, and most likely also autopolyploids, becoming established at their site of origin is very low and depends on many different factors, such as niche separation from their diploid progenitors, population size, fecundity and self-fertilization<sup>54</sup>. This finding seems to support earlier work in plants that suggested that polyploids form new species more slowly and go extinct more quickly than do their diploid relatives, and consequently have lower diversification rates<sup>16,55</sup>. These lower diversification rates are probably particularly applicable to polyploids in stable environments, where most of the diploid progenitors are well adapted and polyploids have difficulty competing<sup>56</sup>. Furthermore, although polyploidy is generally believed to be an important mechanism of sympatric speciation, at least in plants<sup>3</sup>, the conditions for species formation and diversification through WGD are probably not always instantaneous, and selection to strengthen prezygotic barriers in new polyploids is probably crucial for the establishment of polyploid species in sympatry<sup>57</sup>.

However, Schranz *et al.*<sup>58</sup> have proposed the WGD radiation lag-time model, which — on the basis of known numbers of species in certain plant clades — hypothesizes that WGDs do in fact often result in higher diversification rates, but only after a delay of potentially up to several million years. More recently, Tank *et al.*<sup>59</sup> investigated the link between potentially increased rates of diversification and well-documented ancient WGDs, and found significant statistical support for a nonrandom association between WGD events and a delayed increase in rates of diversification. Conversely, other studies — which focused on the WGD in the teleosts, and on the diversity of teleosts and holosteans (gars and bowfin) in the fossil record — failed to detect an association between WGD and significant shifts in rates of lineage diversification, even over very long time frames of a few tens of millions of years<sup>60</sup>. However,

this finding is contrary to the lineage-specific ohnologue resolution (LORe) model<sup>61</sup>, which was proposed in a recent preprint publication. This model suggests that the functional divergence of genes assumed to be responsible for specific adaptations and diversification can be delayed for tens of millions of years owing to delayed rediploidization, which is particularly relevant for autopolyploidy<sup>62</sup>. In the LORe model, the rediploidization process is not completed until after a speciation event, which will result in the independent divergence of ohnologues in sister lineages. Delayed species radiation post-WGD is then explained by the functional divergence of genes in response to, or coinciding with, unique environmental or ecological conditions. As such, LORe, as a product of highly delayed rediploidization, offers a mechanism to explain time lags that occur between WGD events and subsequent lineage-specific diversification<sup>61</sup>. However, it should be stressed that although these different new models are noteworthy, they are very preliminary, and additional supporting evidence is needed to determine the extent to which polyploidy facilitates species radiation. In the absence of a causative link, exactly how polyploidy affects speciation and rates of species diversification remains unclear<sup>16,63–65</sup>.

### WGDs and long-term survival

As described above, polyploids can overcome cytotype minority exclusion, sympatrically speciate and have at least the potential for rapid adaptation owing to their genomic background, which is more plastic than that of diploids<sup>26,37</sup>. Each of these factors could explain the short-term survival of new polyploids and the fact that recent polyploids abound. By contrast, ancient WGDs (that is, those surviving for at least a few tens of millions of years) are much rarer than are new polyploids. Only a few ancient WGDs are known for animals and fungi, although the number in plants is considerably larger. This observation implies that only a minority of polyploids that survive in the short term become established in the long term, which raises the question of which WGDs become established and why? Do they survive purely by coincidence? If so, paleopolyploidies would be expected to be randomly scattered throughout the tree of life. Or is survival associated with very specific times in evolution, such as times of environmental upheaval or periods of extinction? Interestingly, many ancient WGDs are found in separate lineages, while the number of recurrent polyploidy events is usually limited (FIG. 1), which suggests that their distribution is not random and supports the latter theory. Below, we discuss evidence that correlates the long-term survival of WGDs with decisive moments in evolution, such as the origin and diversification of flowering plants, the forest-to-grassland transition and mass extinctions.

**WGDs and environmental instability.** It is widely accepted that, compared with diploids, polyploids have an increased mutational robustness. As discussed above, some evidence suggests that they also have increased environmental robustness and an increased potential for specific adaptation. These properties

#### Neofunctionalization

The process by which a gene acquires a novel gene function after a duplication event.

#### Niche separation

The process by which competing species use the environment differently in a way that helps them to coexist.

#### Sympatric speciation

The process through which new species evolve while inhabiting the same geographical region.

#### Prezygotic barriers

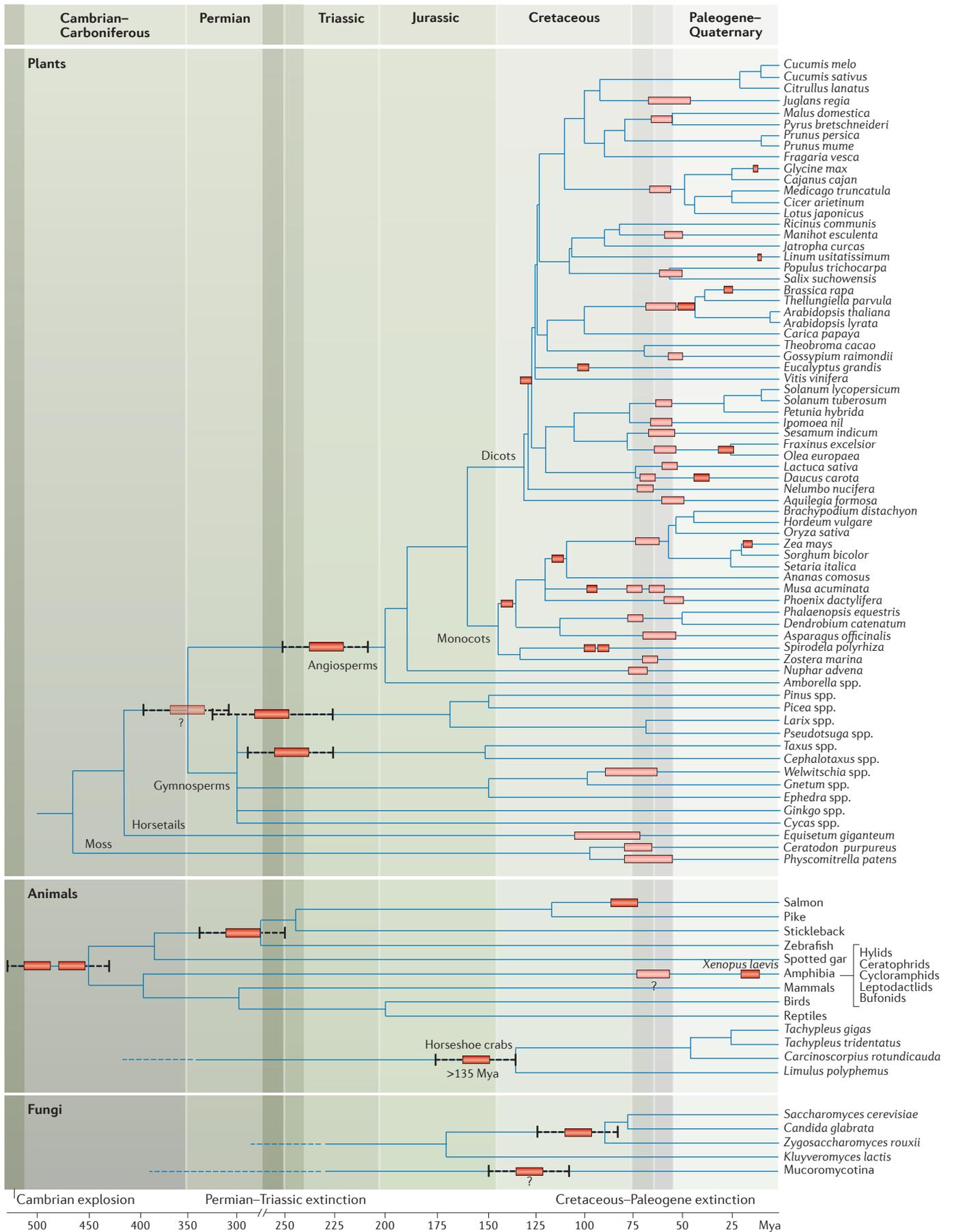
Mechanisms that prevent fertilization from occurring.

#### Ohnologues

Duplicated genes (paralogues) that originate from a whole-genome duplication event.

#### Paleopolyploidies

Polyploidies that have occurred at least several million years ago. Most paleopolyploids have lost their polyploid status through a process called diploidization (the evolutionary process by which a polyploid genome turns into a diploid one) and are currently considered as functional diploids.



**Ecological tolerance**

The range of conditions — or niche breadth — in which an organism can thrive. More tolerant organisms can withstand a broader range of environmental conditions.

might reduce their risk of extinction during periods of environmental turmoil<sup>17,66</sup>. The most compelling evidence that WGDs have a role in avoiding extinction probably comes from flowering plants. Recent analyses of sequence data from a large number of plant genomes and transcriptomes suggest that a wave of WGDs occurred close to the Cretaceous–Paleogene (K–Pg) boundary<sup>15,18,64,67–70</sup> (BOX 2; FIG. 1). The K–Pg boundary is marked by a number of cataclysmic events, such as a meteor impact near Chicxulub (Mexico) and a possibly impact-induced increase in Deccan flood volcanism (India)<sup>71</sup>. These catastrophic events caused major climate change and global warming<sup>72</sup>, and led to the extinction of 60–70% of all plant and animal life, including all non-avian dinosaurs. It has also been previously suggested that polyploidization in animals is correlated with periods of climate change and unstable environments<sup>2</sup>. Interestingly, the environmental instability that occurred during the K–Pg boundary might also have fostered polyploid speciation in the amphibian clade that includes hylids, ceratophrids, cycloramphids, leptodactylids and bufonids, all of which contain multiple independent diploid–polyploid species pairs and diverged ~65 million years ago (Mya)<sup>2</sup>. In fact, all animal taxa in which recent polyploidy events have been described are ectothermic (that is, they do not regulate their body temperature) and are therefore susceptible to changes in the environment. For instance, a striking feature shared by polyploid fish and amphibians is external reproduction in freshwater environments, mainly in regions where temperature fluctuations during the breeding season are common<sup>2</sup>.

The potentially broader ecological tolerance of polyploids relative to that of diploids seems to fit well with a clustering of paleopolyploids around the K–Pg boundary. Other polyploidy events (which are mapped on the phylogenetic tree shown in FIG. 1) might also correlate with extinction events or periods of environmental change, but are much harder to prove. In order to be able to observe a potential correlation and find statistical support, many data points are needed<sup>68</sup>. For instance, although polyploidy in gymnosperms is rare and there are no indications of WGDs in gymnosperms at the K–Pg boundary (with the possible exception of *Welwitschia* spp.<sup>73</sup>), it has recently been suggested that some older WGDs observed in gymnosperms overlap with the Permian–Triassic extinction<sup>73</sup>. Although it is tempting

to speculate that polyploid conifers might have had a better chance of survival and outcompeted their diploid sister species at a time that many of these conifer clades originated, this question might actually never be fully resolved, as there are few remaining branches at the Permian–Triassic boundary and therefore few data points that can be dated (FIG. 1).

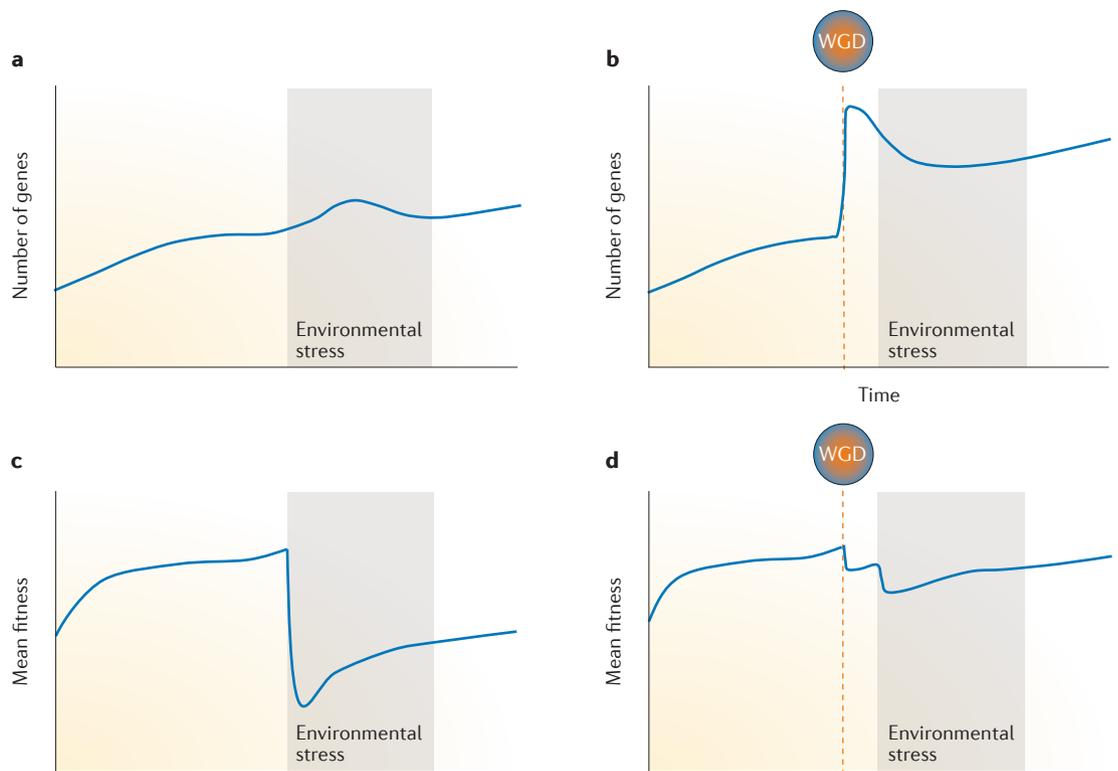
The same holds true for the two rounds of WGDs that occurred during early vertebrate evolution 500–550 Mya, which could have been close to the Cambrian explosion<sup>74</sup>, and the subsequent WGD event in teleosts, which may have occurred close to the Permian–Triassic mass extinction event 252 Mya (REF. 75). Accurate dating of ancient events that might have occurred several hundred million years ago is difficult and prone to errors<sup>14,68</sup>. Furthermore, to paraphrase Soltis and Burleigh<sup>76</sup>, we must be careful not to get ‘carried away’ by the excitement of discovering more and more ancient WGDs, and being tempted to look for correlations. Nevertheless, if we believe the correlation between many of the WGDs in plants and the K–Pg extinction to be real, the majority of the WGDs in plants seem to represent a unique event, which makes ‘coincidental’ WGDs and their establishment even harder to explain.

An example of a more recent wave of WGDs that might be correlated with a period of change, and that is supported by a large number of data points, has been described by Estep *et al.*<sup>77</sup>. These authors found that more than 30% of the ~1,200 species in the grass tribe Andropogoneae were allopolyploids resulting from a minimum of 34 distinct polyploidy events, most of which occurred during the expansion of the C<sub>4</sub> grasslands in the late Miocene period (5.3–11.6 Mya). At this time, grasses using C<sub>4</sub> photosynthesis became important and largely displaced C<sub>3</sub> grasslands following an earlier decrease in atmospheric CO<sub>2</sub> levels in the Oligocene period (23.0–33.9 Mya) and a forest-to-C<sub>3</sub>-grassland transition in the early–middle Miocene period (between 5.3 and ~10–15 Mya)<sup>78</sup>. Thus, polyploidy seems to be correlated with the dominance of C<sub>4</sub> over C<sub>3</sub> grasses and the large-scale displacement of the latter<sup>77</sup>. Interestingly, WGDs in the early–middle Miocene period have also recently been reported for several tribes of the Asteraceae<sup>64</sup>. Here again, global grassland expansion and a changing environment might have created novel open niches for polyploids to invade.

In addition to the previously documented paleopolyploidy events in the crucifer lineage (including, for example, *Arabidopsis* spp.; FIG. 1), transcriptome data obtained by next-generation sequencing recently showed that several species in the Brassicaceae lineage have undergone a more recent (7–12 Mya) polyploidy event. Kagale *et al.*<sup>19</sup> identified eight WGDs that corresponded to at least five independent polyploidy events. Although the Brassicaceae family diverged from other eudicots at the beginning of the Cenozoic era (66 Mya), major diversification occurred only during the Neogene period (2.6–23 Mya). Again, both species divergence and the occurrence of several WGDs seem to be clustered in time at periods characterized by prolonged climatic

◀ **Figure 1 | A phylogenetic tree showing known whole-genome duplications.**

A pruned tree for plants<sup>160,161</sup>, animals and fungi showing the evolutionary relationship between species for which the genome sequence or extensive transcriptome data are available and which are representative for the topic of polyploidy. Mapping of whole-genome duplications (WGDs) described in previous studies<sup>68,73,97,162–172</sup> onto the tree (rectangles) has been performed to the best of our knowledge, with bold black dashed lines reflecting uncertainty in the date of the events. WGDs estimated to be between 55 and 75 million years old (shaded area around the Cretaceous–Paleogene boundary) are indicated by light red rectangles. Mass extinction events are indicated by shaded areas with boundaries 10 million years either side of the predicted date of the event. Mya, million years ago.



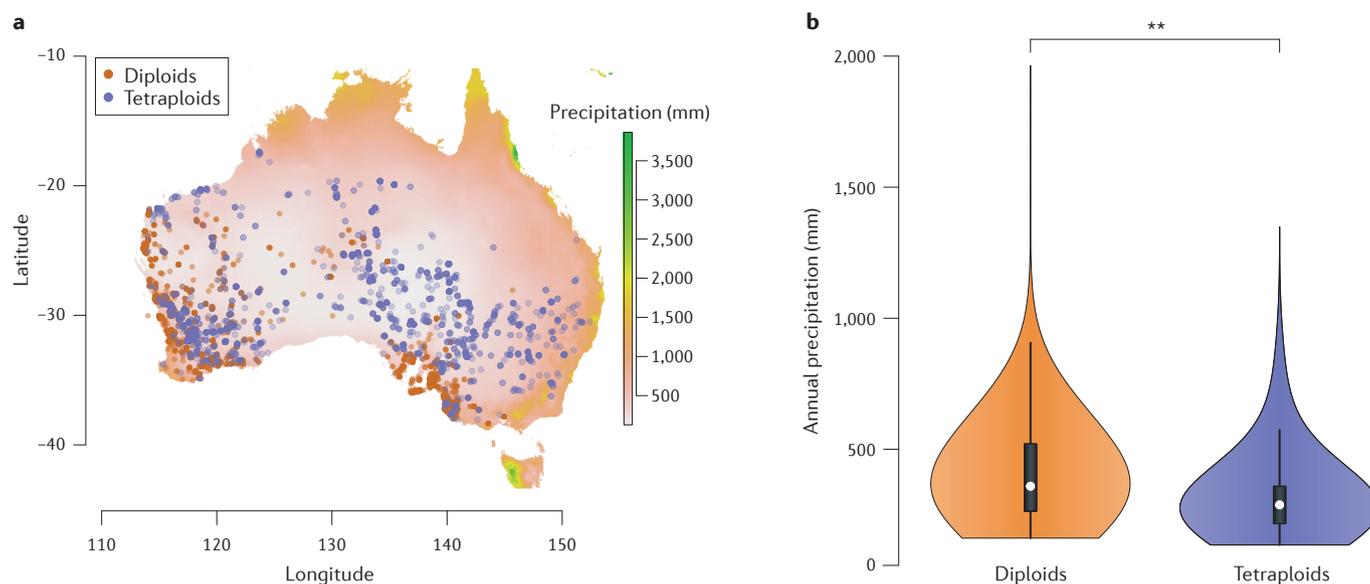
**Figure 2 | A schematic representation of the effects of whole-genome duplication and environmental stress on the evolution of gene number and fitness.** Parts **a** and **b** show the evolution of the number of genes through time in the absence and presence of whole-genome duplication (WGD), respectively, and the potential effect of environmental stress (indicated in grey). In the absence of a WGD, the number of genes might continuously increase with time because of small-scale gene duplication<sup>106,173</sup> (part **a**). Fluctuations might occur in times of environmental stress owing to selection for genes that are important for adaptation. WGD (indicated by the orange dashed line) will initially double the total number of genes (part **b**). Although gene loss following WGDs is usually extensive<sup>106</sup>, the biased retention of genes creates a regulatory and developmental spandrel<sup>107</sup> that might be responsible for a long-term increase in biological complexity (see the ‘WGDs and long-term adaptation’ section of the main text). Parts **c** and **d** show the evolution of fitness through time in the absence and presence of WGD, respectively, and the potential effect of environmental stress (indicated in grey). When the level of environmental stress (drastically) increases, we can expect fitness to decrease (part **c**). However, following WGD (indicated by the orange dashed line), polyploids might have increased adaptive potential (part **d**) owing, for instance, to increased genetic variation and changes in gene expression, which prevent large drops in fitness.

instability. This correlation between WGD events and the diversification of many Brassicaceae species provides further support for the importance of environmental change in the establishment of polyploidization. Finally, many of the extant polyploids that we are familiar with today might be relics of the latest glaciations. Indeed, polyploids (usually allopolyploids) are often found in deglaciated habitats as a result of the hybridization (secondary contact) of closely related species that had earlier become separated as a result of glacial barriers<sup>79,80</sup>.

Neutral processes such as an increase in the formation of unreduced gametes might also make an important contribution to polyploidy at times of environmental upheaval or extinction (FIG. 4). Most polyploids arise through the formation of unreduced gametes, and it is well documented that the production of unreduced gametes can be increased by external stimuli such as stress and a fluctuating environment<sup>2,29,81,82</sup>. In particular, temperature has a pronounced effect on unreduced gamete formation. For instance, higher environmental temperatures increased the production of unreduced gametes in

roses<sup>83</sup>; the induction of cold stress increased the formation of unreduced gametes in *Arabidopsis* species<sup>84</sup> and in *Brassica* spp. interspecific hybrids<sup>85</sup>; and the production of unreduced gametes can be induced in amphibians and fishes by temperature shock<sup>2</sup>. Interestingly, increased levels of fossil unreduced pollen were also observed in a now-extinct conifer family at the Triassic–Jurassic transition, which corresponds to the fourth of the five major extinction events<sup>86</sup>. In addition, atypical gymnosperm pollen<sup>87</sup> and lycophyte spores<sup>88</sup> have been found at the Permian–Triassic boundary that was formed by the third of the five major extinction events. In line with this, the increased formation of unreduced gametes could thus also have been an important factor in the apparent clustering of palaeopolyploidizations at the K–Pg boundary, the fifth and most recent of the last five major mass extinctions<sup>68</sup> (see also BOX 2).

**WGDs and (possible shifts in) ecological niches.** Polyploids are often attributed with a higher tolerance for a broader range of ecological and environmental



**Figure 3 | The distribution of diploid and tetraploid *Neobatrachus* species.** The genus *Neobatrachus* consists of ten extant species of Australian frogs: six that are diploid (*N. fulvus*, *N. pelobatoides*, *N. pictus*, *N. sutor*, *N. wilsmorei* and *N. albipes*;  $2n = 24$ ) and four that are tetraploid (*N. aquilonius*, *N. centralis*, *N. kunapalari* and *N. sudelli*;  $4n = 48$ ). **a** | The geographical distribution of *Neobatrachus* species (data from [AmphibiaWeb](#)). **b** | The occurrence of the *Neobatrachus* species from part **a** combined with climate data<sup>174</sup> shows ecological differences between diploid and tetraploid species, the latter occupying areas with lower annual precipitation (\*\*Mann–Whitney test  $P$ -value  $< 0.01$ ). This suggests that tetraploids are better adapted to drier regions than are diploid species, and could invade new and harsher ecological niches. [Bioclimatic variable 12](#) representing the annual precipitation with 5 mm resolution was averaged with a 0.6-degree radius around each occurrence coordinate using the [R library 'raster'](#). The white dots represent the median, and the black bars represent the interquartile range. Figure courtesy of P. Novikova, Ghent University, Belgium.

conditions than are diploids. Novel and varying phenotypes that may predispose polyploid lineages to colonization success in novel environments (FIG. 3), subsequent adaptation owing to increased genetic variation, and the restoration of sexual reproduction through selfing or apomixis could certainly have been advantageous for exploiting new and changed ecosystems<sup>26,89,90</sup>. For instance, Pandit *et al.*<sup>91</sup> found that polyploids are 20% more likely to be invasive than are closely related diploids when ploidy levels are compared among rare and invasive plant species on a worldwide scale. We have argued before that the availability of new ecological niches could be the single most important determinant of the survival and long-term evolutionary success of a WGD event<sup>17</sup>. The potential for increased phenotypic and genotypic diversity provided by WGDs is less useful when there are no niches in which the new phenotypes or genotypes are advantageous. In stable ecosystems, newly formed polyploids are probably not able to compete with the highly adapted occupants of existing niches, including their diploid ancestors<sup>56</sup>.

However, the extent to which polyploids establish through niche differentiation and whether polyploidy promotes ecological shifts need further investigation<sup>92</sup>. For instance, Glennon *et al.*<sup>93</sup> used statistical tests of niche overlap to compare climate conditions of diploids and young polyploids in a compiled data set of 20 different plant species distributed across North America and Europe. The results did not support frequent or strong climate-based niche shifts by polyploids;

instead, niche conservation and niche contraction were observed. Thus, the authors concluded that other processes (such as short-range or long-range dispersal mechanisms) are more important than are climate-related factors for explaining polyploid establishment and survival. In another carefully executed study, Marchant *et al.*<sup>94</sup> used a variety of niche analysis and multivariate techniques to investigate geographical distribution, niche breadth and niche overlap to infer differences in the patterns of niche distribution between allopolyploids (ten ferns and three angiosperms) and their diploid progenitors. The authors hypothesized that, owing to their increased allelic diversity, the allopolyploids would occupy broader and distinct ecological niches relative to those of their progenitors. However, quite unexpectedly, all allopolyploids (with one exception that clearly showed niche novelty) had a high overlap with at least one of its progenitors<sup>94</sup>. By contrast, a study of niche overlap between four related European primrose species of different ploidy levels used a series of univariate and multivariate analyses combined with modelling techniques and seven bioclimatic variables, and found that polyploids, as expected, occupied ecological niches that differed from those of their diploid relatives<sup>80</sup>. However, unexpectedly, the authors also observed that the polyploids of one species occupied narrower environmental and geographical spaces than did their diploid relative, which is contrary to the idea that polyploids generally have broader niche occupancies than do diploids.

## Box 2 | Polyploidy: a spandrel of occasional sex

Accumulating evidence indicates that polyploidy can increase mutational and environmental robustness, which might increase the potential for specific adaptation in response to changing environmental conditions or reduce the risk of extinction during periods of environmental upheaval. Recently, Freeling<sup>158</sup> proposed an interesting alternative hypothesis about how polyploid plants might be able to survive periods of mass extinction (FIG. 1; Cretaceous–Paleogene boundary). Freeling started from the observation that new polyploids encounter major problems during sexual reproduction owing to meiotic difficulties<sup>24</sup>, which reduce fitness if organisms reproduce sexually. Furthermore, an asteroid hitting Earth would cause the depletion of the Earth's protective ozone layer<sup>159</sup>, in turn leading to a serious increase in surface ultraviolet B irradiance, which would cause the mutation and breakage of DNA. However, if the polyploid could shield its reproductive meristems and avoid meiosis altogether, it would increase its chances of survival<sup>158</sup>. One way to achieve this would be to reproduce asexually for a while by, for instance, budding underground or under water. During or after this period of 'hiding out' during unfavourable conditions, the polyploid can undergo diploidization, which is necessary for re-establishing accurate meiosis. When meiosis has been re-established, the 'rediploidized' polyploid (now functioning as a diploid) might then again produce flowers and reproduce sexually. Freeling thus proposes that the observed pattern of clustered whole-genome duplications at times of mass extinctions can be explained by considering polyploidy as a mere spandrel of an asexual life stage. Once the environment has normalized, the now-diploidized polyploid can reproduce sexually, and this is necessary for its long-term evolutionary success. Of course, non-polyploid asexuals should also be able to survive mass extinctions by hiding out temporarily, but they are expected to be outcompeted by the polyploids, which have greater adaptive potential and increased colonization success (see REF. 158 and the main text).

WGDs that occurred early in the evolution of flowering plants<sup>95</sup>, or before the divergence of eudicots<sup>96</sup> or monocots<sup>97</sup>, do not — as far as we can tell — coincide with periods of mass extinction. It is also questionable whether they rose to ecological dominance by filling niches that became available after a drastic change of the environment. Instead, a more credible explanation here is that these polyploids and their descendants filled niches that might already have existed but that remained largely unoccupied in the past because the necessary phenotypic traits for survival in that niche had not yet been developed. In this case, WGDs might have led to so-called key innovations such as the flower<sup>95,98</sup>, facilitating diversification and radiations, and the invasion of previously unoccupied niches at later times.

**WGDs and long-term adaptation**

So far, we have discussed how, in their initial stages of establishment, polyploids will often have a small population size and restricted distribution, and consequently a higher risk of extinction than do diploids, at least in 'normal' or stable circumstances. By contrast, in more challenging environments, polyploids may have a selective advantage and start to outcompete their diploid progenitors to attain a considerable population size and range; compared with their diploid progenitors, polyploids might have different characteristics that reduce their relative risk of extinction. However, the question remains about whether polyploidy or WGD has specific long-term implications for evolution, aside from the selective advantage leading to the initial short-term survival and establishment of polyploids. Here, we discuss biased gene retention and the role it might have in long-term adaptation.

**Biased gene retention following WGD.** Duplicate genes that originated in the two successive ancient WGD events (~500–550 Mya) in vertebrates (FIG. 1) have been shown to still make up ~30% of the genes in the human genome<sup>99</sup>. These genes are thought to be particularly sensitive to dosage balance, unlikely to vary in copy number, and more frequently associated with disease than are non-duplicate genes<sup>100</sup>. Subsequent studies suggested that these duplicate genes are probably heavily susceptible to dominant deleterious mutations<sup>101</sup>. Functionally, these genes are involved in organismal complexity, and they have important roles in signalling and development, as well as in transcriptional regulation. Recently, Singh *et al.*<sup>102</sup> performed a comparative analysis of six vertebrate and six invertebrate species (the latter being the unrelated outgroup), and identified ~2,000 vertebrate ohnologue gene families. These ohnologues were extremely conserved in terms of copy number, with almost all remaining as four copies in the six vertebrate genomes<sup>102</sup>. Ohnologues were approximately threefold more likely than non-ohnologues to account for cancers and autosomal dominant diseases, and up to eightfold more likely to encode a protein with autoinhibitory protein folds<sup>102</sup>. So, it seems that at least in vertebrates, genes involved in form and development are often under negative or purifying selection to retain them as duplicates because changes to these 'dangerous duplicates' (REF. 101) are deleterious to the organism. Further support for this dominant-negative hypothesis for retention comes from the rainbow trout WGD (dated to ~80 Mya), following which genes returned to a singleton status in at least 50% of cases, but so-called dangerous genes (in which deleterious changes are not tolerated) were retained in duplicate copies<sup>103</sup>. A recent study on the tetraploid frog *Xenopus laevis* (an allopolyploid that is functionally diploid owing to lack of recombination between homoeologues) once again demonstrated that genes retained in multiple copies in all lineages after the ancient vertebrate and teleost WGDs were also more likely to be retained as ohnologues in *X. laevis* than were other genes<sup>104</sup>.

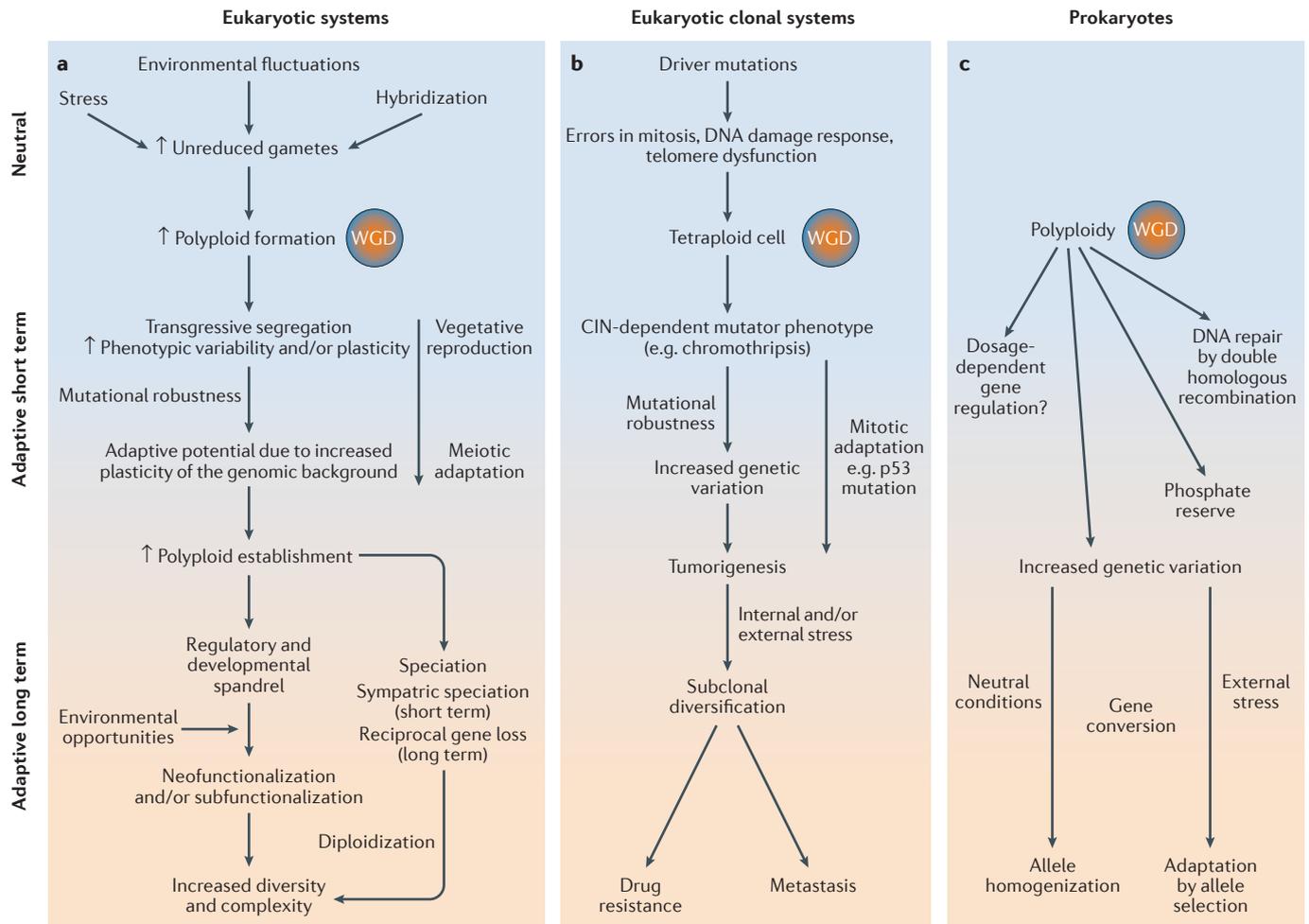
We learn from vertebrates that some WGD-derived duplicate genes must obligatorily be retained as duplicates. The question remains whether, when many independent ancient WGDs are considered, the same genes are repeatedly maintained as duplicates for long periods of evolutionary time. Flowering plants perhaps offer a unique system in which to study the survivability of duplicated genes owing to the many independent WGD events observed in these species around the K–Pg boundary. Li *et al.*<sup>105</sup> recently investigated the fate of duplicated genes for almost 40 different flowering plant species, all of which have experienced one or more ancient WGD events. It was observed that gene loss following WGD strongly deviated from a stochastic model, with the majority of genes rapidly returning to a single-copy status<sup>105</sup>. Conversely, some genes were found to be consistently present in multiple copies. In general, these multi-copy genes belong to gene families that are involved in conditional responses to biotic and abiotic stress, and are important for local adaptation.

**Key innovations**

Important adaptations that lead to subsequent species radiation or that are of major importance for the success of a taxonomic group.

**Dosage balance**

The state in which the stoichiometry between all interacting partners (that is, proteins) is maintained.



**Figure 4 | Polypleidy in different systems. a** | Both neutral and adaptive processes can contribute to the formation and establishment of polyploids in clonal and non-clonal eukaryotic systems. Environmental change or stress can increase the formation of unreduced gametes, while other processes such as hybridization can also contribute to an overall increase in the frequency of unreduced gametes in the total gamete pool. However, for polyploids to survive and become established, selection for specific traits resulting from increased phenotypic variability and plasticity is probably still necessary. Transgressive segregation (in which progeny have more extreme phenotypes than do parental lines) could be important here. In addition, the specific adaptation of more crucial cellular processes, such as meiosis, might be necessary for polyploids to become successful in the longer term<sup>175</sup>. Note that, in both the neutral and adaptive scenario, the environment has an important role in polyploid establishment. **b** | Adaptive processes following a whole-genome duplication (WGD) event in eukaryotic clonal systems, such as cancer. WGD usually originates through mitotic errors, sometimes as a result of driver mutations, and results in a tetraploid state. Further mutations affecting, for example, the DNA damage response (for example, p53 mutations) enable polyploid cells to further proliferate. However, cell divisions are unstable (leading to chromosomal instability (CIN)) and give rise to aneuploidy. As aneuploidies often result in lethal phenotypes, mutational robustness provided by the polyploid background allows near-tetraploid cells to tolerate aneuploidy better than do diploids. Such aneuploidy increases genetic variation, which can then result in the origin of tumorigenesis and further adaptive events, such as drug resistance and metastasis. **c** | Hypothetical adaptive effects of polypleidy in prokaryotes (and possibly asexual eukaryotes<sup>145</sup>). Many prokaryotes display growth-phase-dependent polypleidy levels. In prokaryotes, polypleidy can contribute to the direct survival of the individual (for example, by serving as a phosphate reserve or by protecting against highly mutational environments) but can also contribute to long-term survival during different selection regimes by increasing genetic variation. Gene conversion would have an important role in establishing the adaptive benefits of polypleidy in prokaryotes.

Irrespective of whether they are created by WGD or small-scale duplication, duplicated genes belonging to these gene families are quickly put to novel use<sup>106</sup>. Another group of genes that often show biased retention following WGDs encode proteins that act in multiprotein complexes and/or have important roles in signalling, development or transcriptional

regulation<sup>105</sup>. In addition to being explained by the dominant-negative hypothesis of retention, this pattern of gene loss and retention can be explained by dosage-balance constraints, and by selection against the loss of individual components of completely duplicated macromolecular complexes and/or pathways that would disrupt their overall stoichiometry<sup>106–109</sup>.

**Long-term effects of biased gene retention.** The strongly biased retention of regulatory and developmental genes subsequent to WGD is sure to have important consequences for evolution on the longer term. Initially, the retention of these particular genes may be considered an evolutionary spandrel: that is, a neutral by-product<sup>107</sup> (FIG. 4). However, eventually, selection to maintain dosage balance and stoichiometry will relax over time, allowing duplicated networks to be rewired, and to evolve novel functionality and increase biological complexity<sup>110,111</sup>. Indeed, recent work considered the potential impact of WGDs on the evolution of transcription factors in metazoans and showed that the longer retention time of transcription factors following WGDs was necessary for them to gain novel functions<sup>112</sup>. Therefore, we can consider the long-term or delayed impact of WGDs on innovation and diversification as the product of non-adaptive negative selection (which leads to the biased retention of classes of genes such as transcriptional regulators); neutral processes (such as, for instance, domain rearrangements); and subsequent positive selection (such as neofunctionalization or subfunctionalization) of genes and networks. In conclusion, provided that there is sufficient time for the polyploid to survive a WGD, there is indeed a plausible mechanism by which the neutral disentanglement of dosage-sensitive components and the freedom to explore complexity can result in adaptive diversity, leading to specialization and possibly speciation (FIG. 4). However, widespread speciation after WGD would therefore typically be a delayed phenomenon<sup>17</sup>, which would also be consistent with the WGD radiation lag-time model proposed by Schranz *et al.*<sup>58</sup>.

### Polyploidy in clonal systems

The impact of polyploidy on the adaptive potential of clonal systems also seems to be much more prevalent than was initially appreciated. Despite the fundamentally different mechanisms by which polyploidization results in increased adaptive potential in clonal versus non-clonal systems, some striking similarities exist in the impact polyploidization has on increasing genetic variation and mutational robustness.

**Programmed polyploidy.** Sometimes polyploidy does not affect whole organisms but arises in the somatic cells of otherwise diploid organisms. Somatic polyploid cells can arise either by cell fusion or when cell division aborts before cytokinesis<sup>113</sup>. Such cells are described as endopolyploid, and they often have ‘programmed’ roles in normal development and stress responses<sup>37</sup>. Well-known examples of specialized endopolyploid cells include fibres and leaf hairs in plants<sup>114</sup>, or megakaryocytes and glial cells in animals, and wing scale cells in moths and butterflies<sup>115,116</sup>. In mammals, hepatocytes are particularly prone to polyploidization in response to DNA damage that would cause most other cells to undergo apoptosis, and the frequency of tetraploid and octoploid hepatocytes steadily increases during liver growth<sup>117</sup>. Although the benefits of programmed polyploidy are not fully understood, the ability to generate

endopolyploid cells is probably an important adaptation when rapid growth or large cell size is required, or in tissues or cell types for which mitotic division would be deleterious for structural reasons<sup>117</sup>. Endopolyploidy can also be induced by variable environmental conditions, such as drought or salt stress. In this respect, it is interesting to note that somatic WGD might contribute to stress resilience in plants, which might even translate into the whole-organism effects described above (see the ‘WGDs and short-term adaptive potential’ section). For instance, it has been demonstrated that root endopolyploidy in sorghum is associated with salt tolerance<sup>118</sup>, which suggests that the ability to induce endopolyploidy is directly responsible for the resistance to salt, potentially owing to cell size changes in the roots. The increased salt tolerance of *A. thaliana* autopolyploids<sup>49</sup> compared with diploids might, at least in part, be explained by similar processes<sup>119</sup>.

**Unprogrammed polyploidy and cancer.** Unprogrammed WGDs also occur; they are not part of normal development and, for instance, characterize a substantial proportion of human tumours. Aneuploid cancers with triploid or near-tetraploid genomes probably originate from a transient tetraploid intermediate<sup>120</sup>. Such transient polyploidy states have been observed in several tumour types at early stages of tumorigenesis<sup>120–122</sup>. The origin of tetraploidy in tumours has been attributed to cell fusion events, or errors in the progression of or exit from mitosis, or has been thought to occur as a consequence of persistent damage response or telomere dysfunction<sup>117</sup>.

Transient tetraploids display chromosomal instability (CIN), and frequent chromosomal mis-segregation results in the acquisition of aneuploidy over short periods of time<sup>117,123</sup>. In addition, increased polyploidy in cells has been associated with a higher propensity for developing chromothripsis. In contrast to the gradual evolution of aneuploidy, chromothripsis leads to massive DNA structural rearrangements in localized chromosomal regions as the result of a single catastrophic event<sup>124</sup>. Owing to their genomic instability, transient tetraploids and aneuploids proliferate better in cells with disrupted apoptosis or cell cycle checkpoint pathways than in normal healthy cells. Thus, somatic mutational events — for instance, in tumour suppressor proteins such as adenomatous polyposis coli (APC; mutations in which lead to colon cancer<sup>125,126</sup>), retinoblastoma-associated protein (RB) or p53 — often precede<sup>127</sup>, or are associated with, a WGD event<sup>117,128,129</sup> (FIG. 4).

Tetraploids and their subsequent aneuploid states rapidly give rise to adaptive phenotypes resulting in tumorigenesis<sup>117,121,122</sup> or drug resistance (as reviewed in REF. 120). Aneuploidies that result in adaptive drug resistance have also been generated through a transient polyploid state in ‘clonal’ yeasts such as *Cryptococcus neoformans* and *Candida albicans*<sup>130</sup>. These findings indicate that the transient tetraploid state is a ‘gateway karyotype’ in clonal systems that, like in plants, increases genetic variation and adaptive potential; however, in contrast to plants, it does so mainly by promoting

#### Spandrel

In evolutionary biology, a spandrel is a by-product of the evolution of some other characteristic or trait, rather than a direct product of adaptive selection. At later stages of evolution, such a by-product can become (that is, can evolve into) an important adaptation.

#### Aneuploid

A term that describes a cell or organism that has an abnormal number of chromosomes. For instance, in humans, trisomy 21 (an extra copy of chromosome 21) is a form of aneuploidy.

#### Chromothripsis

The phenomenon by which potentially thousands of chromosomal rearrangements occur in a single event in localized and confined regions of the genome.

aneuploidy<sup>117,120</sup>. Indeed, aneuploidy and chromosomal duplications have been associated with high adaptive potential in clonal systems<sup>120,131,132</sup>. For instance, experimental evolution studies in yeast have shown that specific chromosome duplications can confer a fitness advantage during stressful conditions<sup>131,133–135</sup>. Thus, changes in copy number result in altered gene expression that can give rise to an adaptive phenotype if appropriate genes are amplified<sup>120,134</sup>. In cancers, for instance, aneuploidy (resulting mainly from CIN) would contribute to tumorigenesis and progression by promoting the loss of tumour suppressors, the amplification of oncogenes or the formation of fusion genes<sup>128,136,137</sup> (FIG. 4).

However, WGD does not only increase adaptive potential by providing a gateway karyotype that gives rise to CIN and increased genetic variation. While ~90% of solid tumours and ~50% of haematopoietic cancers are aneuploid and display CIN<sup>137</sup>, only ~37% would have undergone a WGD according to a pan-cancer analysis<sup>136</sup>. Nevertheless, near-tetraploid cells have been shown to have a higher tumorigenic capacity than do near-diploid aneuploid cells<sup>138</sup>, and WGD in cancer is often associated with poor prognosis and disease relapse (see REF. 138 and references therein). In addition, several studies have shown that resistance to targeted therapy in tumour cells is associated with the origin of polyploidy<sup>120</sup>. Also, it has been shown in yeast that tetraploids adapt faster than do haploids or diploids<sup>134</sup>. Part of this higher evolvability in tetraploid clonal cells can be attributed to the fact that the higher polyploidy itself increases mutational robustness against further genetic alterations because the additional genome copies will compensate for gene deletions or inactivating genetic variants<sup>117,120</sup>. Although CIN and aneuploidies can drive tumorigenesis or adaptive phenotypes, they are often more likely to generate a deleterious phenotype and/or give rise to proteotoxic stress, which is caused by the increased number of proteins that need to be folded, thereby exceeding the protein-folding capacity of a cell<sup>137</sup>. However, the polyploid state resulting from a tetraploid intermediate is believed to buffer the effects of aneuploidies; dosage effects of an aneuploidy are expected to be relatively less severe in a  $4n$  than in a  $2n$  background, and many of the extreme phenotypes resulting from aneuploidy are attenuated in polyploid cells<sup>132</sup>. As a result, tetraploids are expected to generate a relatively higher genetic variability by providing higher tolerance for CIN, as was indeed shown by Dewhurst *et al.*<sup>138</sup> in the context of colorectal cancer. This higher tolerance might also explain why chromothripsis could be associated with hyperploid cells but not with diploid cells<sup>124</sup>. Consequently, some of the adaptive genetic variation is also expected to depend on the polyploid background and its capacity to buffer the detrimental effects of aneuploidy. This ploidy-dependent beneficial effect of aneuploidies was indeed confirmed by Selmecki *et al.*<sup>134</sup>, who showed that specific adaptive aneuploidies only conferred a fitness effect in a  $4n$  background but not in a  $2n$  background.

Last, because polyploidy buffers the effects of partially recessive deleterious mutations, such mutations can accumulate and create standing variation that might

be adaptive in a new environment (for example, drug resistance<sup>123</sup>) or that allows cells to explore adaptive solutions involving epistatic interactions<sup>139</sup>. As such, transient tetraploidy can, by generating and buffering aneuploidy, result in improved long-term adaptation (FIG. 4). Interestingly, Selmecki *et al.*<sup>134</sup> showed that  $4n$ -evolved clones that became near-diploid had a higher fitness than did  $2n$ -evolved clones. Temporal studies in lung cancer showed that a WGD event preceded large-scale subclonal diversification, which indicates that WGD also accelerates adaptation at later stages of cancer evolution<sup>127</sup> (FIG. 4).

**Polyploidy in prokaryotes.** In contrast to what has generally been assumed, recent studies have shown that polyploidy is not all that uncommon in Bacteria and Archaea<sup>140–142</sup>. Polyploidy seems to have evolved independently several times in different groups of prokaryotes for different evolutionary reasons<sup>141,143</sup>. As polyploidy in prokaryotes has mostly been studied in the context of Bacteria and Archaea that live in extreme conditions<sup>143</sup>, some of the proposed benefits of polyploidy might be confined to these extremophiles; such benefits include providing resistance to severe conditions that introduce double-strand DNA breaks (such as X-ray radiation and desiccation), or providing phosphate storage that would allow cells to divide a few times in the absence of external phosphate (FIG. 4). However, the proposed benefits that relate to gene dosage and mutational robustness might be widespread in the bacterial kingdom, although so far, little experimental evidence is available<sup>143</sup>. Just like in higher eukaryotes, polyploidy in prokaryotes would result in gene redundancy and the subsequent mutational robustness would allow gene copies to change without losing the wild-type information from the remaining copies. The standing variation thus generated might allow cells to grow in unfavourable conditions that inhibit the growth of the homozygous wild type. Gene conversion (that is, the non-reciprocal transfer of information between homologous sequences through homologous recombination) would have an important role in establishing the adaptive benefit of polyploidy-dependent mutational robustness in prokaryotes<sup>144</sup>, and maybe also in (some) eukaryotes<sup>145</sup>. Gene conversion equalizes genome copies to yield a genome that is homozygous for functional genes. This way, favourable alleles could be selected for in selective conditions while harmful ones would be removed, even in non-selective conditions. This prevents the accumulation of deleterious alleles that, in the long term, would drive the clonal population to extinction. Gene conversion is of particular importance in those polyploid organisms that more or less randomly distribute chromosomes between daughter cells because such a random assortment does not guarantee that compensatory alleles located on different chromosomes will be co-inherited in a subsequent generation. Random assortment thus often results in the accumulation of deleterious recessive (or partially recessive) alleles that will result in unviable offspring (a situation termed segregation load), and in the lack of evolutionary constraints to select for combinations of beneficial alleles located on

#### Standing variation

The presence of two or more alleles at a locus in a population that have not yet been fixed in the population.

different chromosomes. The evolution of more accurate means of chromosome distribution during cell division (that is, the emergence of mitosis), as recently suggested by Markov and Kaznacheev<sup>146</sup>, could provide an efficient mechanism by which to protect ancestral amitotic polyploids against the accumulation of a segregation load.

**Conclusions**

The ability to sequence entire genomes and transcriptomes at low cost, together with the potentially large impact of WGDs on speciation and biodiversity dynamics, ecology and evolution in general, has generated much interest in polyploidy<sup>147–149</sup>. One of the main conclusions from reviewing the vast literature on polyploidy and WGDs is that the consequences of polyploidy are complex and variable, and seem to differ greatly between different species<sup>150–152</sup>. Additional research will be required to reconcile the short-term effects of polyploidy with the subsequent long-term evolution and successful establishment of polyploids<sup>9,76,94,148</sup>. However, there seems to be accumulating evidence that links short-term polyploid establishment and survival to periods of environmental and ecological upheaval. If true, this of course has the potential to help to explain the apparently contradictory evolutionary fates of polyploids: polyploidy is usually an evolutionary dead end, except in ‘abnormal’ circumstances when polyploids might have an evolutionary edge over non-polyploids. Furthermore, once

established, polyploidy might also have important consequences for long-term evolution owing to the biased retention of duplicated genes. As regulatory and developmental genes are specifically retained, linking WGD with important evolutionary transitions and a general increase in biological complexity — as proposed more than 40 years ago by Susumu Ohno<sup>7</sup> — might not be so far-fetched.

Cancer is increasingly seen as an evolutionary system in which polyploidy is being ascribed an increasing role. Indeed, in cancer and other eukaryotic clonal ‘systems’ such as yeast, polyploidy plays a crucial part in increasing the adaptive potential during periods of extreme stress by providing mutational robustness and increasing the adaptive effects of CIN. Polyploidy is prevalent even in prokaryotes, which for a long time were believed to be strictly monoploid. In prokaryotes, polyploidy is assumed to mediate gene dosage regulation and/or to provide cells with sufficient standing variation to quickly adapt in response to changing conditions or environments.

Thus, the impact of WGD on evolutionary events and adaptations might be much more widespread than was initially thought. Consequently, a better understanding of polyploidy and WGD will undoubtedly be important in enabling us to tackle future challenges in areas as diverse as global warming and climate change, agriculture and crop domestication<sup>153,154</sup>, natural selection and adaptation, and cancer research.

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## Competing interests statement

The authors declare no competing interests.

## FURTHER INFORMATION

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