Trends in Genetics

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Spotlight

Duplicated gene networks promote 'hopeful' phenotypic variation

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The consequences of whole-genome duplication (WGD) remain elusive. A new study by Ebadi *et al.* simulating duplicated gene networks predicts that WGD immediately generates autopolyploids with extreme phenotypes and increases phenotypic variance. Such theoretical work calls for new experimental studies addressing to what extent WGD may be beneficial under environmental changes.

Gene duplication is repeatedly observed throughout the radiation of eukaryotes. Its consequences for the functioning and adaptive evolution of organisms, however, remain largely elusive, especially when affecting sets of interacting genes such as following WGD. Ebadi *et al.* [1] recently advanced this field by simulating the duplication of gene networks made of 'input' genes (i.e., sensing a stimulus), 'regulatory' genes (i.e., controlling the activity of other genes), and 'output' genes (i.e., producing a measurable phenotype) to assess the impact of WGD on phenotypic variation. The authors generated random and scale-free networks of genes with fixed interactions, being enriched in biologically relevant feed-forward loops and devoid of never-ending loops to assess signal propagation across the network towards outputs. To simulate WGD, all genes were simply duplicated so that an ancestral gene A regulating, for example, genes B and C presents an A′ duplicate that, as A does, regulates B′ and C′ as well as B and C. Although such modeling of duplicated networks is inadequate to predict outcomes of allopolyploidy that further involves hybridization between divergent sets of genes (i.e., not presenting full redundancy), and hence unpredicted interactions such as dominance, it mimics immediate consequences of WGD and hence the first generation of autopolyploids [2]. The few empirical studies that adequately dissected changes in gene expression caused by hybridization versus WGD reported limited transcriptional rewiring in response to only the later (e.g., [3]) and hence appear consistent with the assumptions of the modeling framework by Ebadi *et al.* [1].

Independently of their size, duplicated gene networks were shown to yield extreme output values, being increased in the same direction by ca. 30% as compared to corresponding non-duplicated networks. In other words, WGD is predicted to result in exaggerated phenotypes in autotetraploids as compared to their immediate diploid progenitors. Fitting these expectations, cytological and anatomical studies of experimental autopolyploid plants generated in the laboratory by WGD commonly present a corresponding 'gigas effect'. Nevertheless, molecular underpinnings of the relationships between gene duplication, dosage, and phenotypes across functional networks remain elusive. Empirical tests of the prediction that duplication promotes increased or decreased levels of gene expression across networks to support extreme phenotypes indeed remain challenging due to the myriad changes in cell and transcriptome sizes (i.e., nucleotypic effects) that affect comparisons of samples differing by their ploidal level [4].

Simulations of Ebadi *et al.* [1] further assessed phenotypic outcomes of duplicated gene networks in response to variation in input values (e.g., mimicking environmental changes). The average phenotypic variance among populations of duplicated networks is predicted to be considerably higher than that of ancestral non-duplicated networks or unrelated networks with a similar number of non-duplicated genes. Although supporting that a network architecture consisting of totally redundant, duplicated genes enlarges the phenotypic space that can be reached, the corresponding prediction that a population of nascent autopolyploids presents transgressive variation compared with diploid ancestors has rarely been tested empirically. Recent experiments using *Arabidopsis thaliana* have shown important and sometimes discrepant consequences of WGD among levels of biological organization, with enlarged cells increasing storage capacity or drought tolerance in autopolyploid plants, but also reducing the biomechanical stability of their stems [5]. Further investigations using experimentally duplicated plants (e.g., [6]) will be necessary to unravel the molecular and functional consequences of WGD. In particular, future experimental work will have to quantify variation in the phenotypic responses to WGD, assessing the extent to which nascent autopolyploids match *in silico* predictions and immediately benefit from a higher adaptive potential than previously thought.

Exaggerated traits and increased phenotypic variance generated by WGD may be of limited benefit under stable environmental conditions (i.e., constrained input signals) but could otherwise promote survival (Figure 1). It may contribute to explaining the association between non-random WGD events in time and the occurrence of major environmental crises [7], despite pervasive challenges with molecular dating [8]. At least, that gene redundancy inherent to WGD-derived networks increases the phenotypic variance in autopolyploids, and hence supports their better performance under unpredictable environments, may rule the process beyond exceptions inherent to theories such as catastrophism. That the duplication of gene networks can

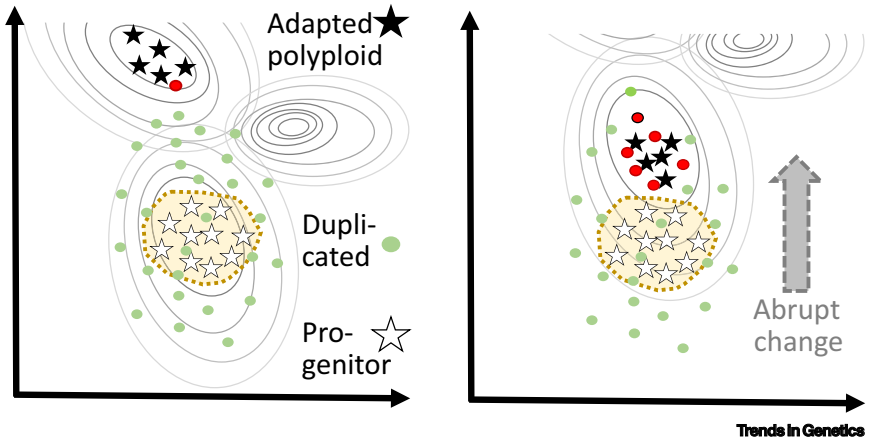

Figure 1. Autopolyploid speciation under stable (left) and changing (right) conditions. An adaptive landscape is shown as lines of equal fitness across possible phenotypes (outputs of gene networks) summarized along the x and y axes. The duplication of progenitors (empty stars) immediately yields individuals (dots) presenting increased phenotypic variance, with 'hopeful monsters' depicted in red. Post-duplication evolution yields adapted polyploid phenotypes (filled stars).

be related to saltational (as opposed to gradual) evolution, resulting in autopolyploids to be considered as 'hopeful monsters', seems premature, however. Of course, by doubling all chromosomes and genes at once, WGD certainly fits the intended meaning of a 'macromutation' or 'systemic mutation' *sensu* Goldschmidt. However, it is well known that mutations show a distribution of phenotypic or fitness effects ranging from infinitesimal to large (usually lethal) consequences. What is virtually unknown is to what extent WGD breaks genomic constraints imposed by pleiotropy as expected for 'hopeful monsters' that shall typically show considerable phenotypic deviation from ancestors while maintaining a high fitness. Although deeply embedded in gene networks, pleiotropic genes concomitantly dealing with multiple phenotypes, and hence being at the heart of biological trade-offs, have not yet been sufficiently investigated in the context of WGD. As all gene products remain balanced immediately following WGD, transgressive traits in the first generation may seem unlikely to overshoot the top of adaptive peaks to which their ancestors were adapted and generate phenotypic variation supporting breakthrough towards an independent adaptive peak in a single step (i.e., saltation). As advocated by Ebadi *et al.* [1], WGD-derived monsters could mostly be hopeful under conditions of environmental turmoil. Such necessary coincidence of improbable events grounded in both genetic (i.e., an adapted monster) and environmental changes (i.e., during a catastrophic time) may seem unlikely to generally drive the origin of divergent, pre-adapted species [9] and may further look at odds with polyploidy being regularly associated with the origin of new plant species [10]. By contrast, immediate postzygotic reproductive isolation conferred by WGD, although not necessarily generating new species in a single step, is permanently promoting adaptive divergence among gene pools differing in ploidal level and may hence represent a regularly efficient driver of polyploid evolution across generations.

How much duplicated gene networks support adaptive evolution beyond the first generation after WGD, and possibly promote the successful radiation of autopolyploid lineages, remains to be further examined. Enabling networks to explore novel regulatory interactions and activities, duplicated genes promote robustness in the face of accumulating mutations and may hence facilitate the evolution of new phenotypes while ancestral functions are preserved. Promising simulation frameworks have been proposed to predict post-WGD genome evolution under adaptive scenarios (e.g., [11]) and could certainly accommodate advances proposed by Ebadi *et al.* [1] to enable clear predictions beyond the first generation following WGD. Although it is increasingly clear that selection caused by the necessity to maintain dosage balance among interacting genes just after WGD is strongly constraining functional divergence among duplicated genes and likely promotes evolutionary stasis over generations, the drivers of long-term compensatory changes among initially coordinated genes remain contrastingly elusive. More generally, it is largely unknown whether factors causing the success of polyploids reside in WGD *per se* versus the post-WGD resolution of duplicated gene networks. In particular, knowledge of how ancestrally pleiotropic genes are being optimized across duplicated networks, and how this potentially supports innovation, looks desirable to improve predictive models of genome evolution and, more generally, shed light on the adaptive potential of duplicated gene networks. Accordingly, further theoretical work building on duplicated gene networks through time would be beneficial in setting clear predictions to be tested empirically using the myriad omics approaches that currently facilitate the mapping from genome to phenome in polyploid species of various ages [12].

Declaration of interests

The author declares no competing interests.

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