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Opinion

Genome Stability and Evolution: Attempting a Holistic View

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The reason why the DNA content, chromosome number and shape, and gene content of eukaryotic genomes vary independently remains a matter of speculation. The same is true for the questions of whether there is a general tendency for increase or decrease of genome size and chromosome number and whether genome size and/or chromosome number have an adaptive value and, if so, what this value is. Here we assume that three strategies of genome evolution (shrinkage, expansion, and equilibrium) have developed to find the optimal balance between genomic stability and plasticity. We suggest various modes of DNA double-strand break (DSB) repair in combination with whole-genome duplication (WGD) and dysploid chromosome number alteration to explain the different strategies of genome size and karyotype evolution.

Background and Aim

The nuclear genetic information of eukaryotic organisms is contained in an organism-specific number of linear chromosomes, the karyotype. The number of genes in eukaryotes varies from ~5000 (baker's yeast) to > 100 000 (hexaploid bread wheat), the number of chromosome pairs ranges from one (the ant *Myrmecia pilosula*) to > 100 (some ferns), and the haploid and unreplicated nuclear DNA content (the 1 C value) can vary by more than 2400-fold in flowering plants (Figure 1). The apparently uncorrelated ratio of genetic complexity to nuclear DNA content is called the 'C-value paradox' [1] or, more recently, the 'C-value enigma' [2] and the reason for it remains a matter of speculation. The same is true for the questions of whether there is a general tendency for increase or decrease of genome size and whether genome size and karyotype structure have an adaptive value and, if yes, what that value is (for a review see [3]). The evolutionary importance of the distinct mechanisms that mediate chromosome number alteration is also unclear.

Here we discuss strategies for the evolution of genome size and chromosome number in the context of genome stability. While genome stability is important for maintenance of optimally adapted phenotypes, perfect stability would prevent further adaptation to changing environments. Therefore, for optimal fitness a balance between maintenance of a well-adapted genome and a certain degree of variability within a population (for potential need to readapt to changing environments) seems to be a requirement. Depending on the species and the stability of its typical environment, the average mutation frequency may differ. As a potential outcome of mutations (including ploidy and chromosome structural mutations as well as transposon mobility and indels), the genome size may vary. Intrapopulation genome size variations have been observed in, for example, Rotifera (7% variation [4]), *Drosophila melanogaster* (13% variation [5]), and many plant species [6], such as maize ([7] and older references therein).

Trends

Despite recent developments in genomics it remains unclear why gene content, chromosome number, and genome size vary independently of each other. Is there a tendency for genome size or chromosome number to increase or decrease over time? Does genome size or chromosome number have an adaptive value and, if so, what is that value?

Genomes need a balance between required stability and some degree of variability sufficient for optimal fitness of their carriers.

Recent genomic and cytogenomic approaches indicate that, besides sex, whole-genome duplication and erroneous DNA double-strand break repair are the main sources of genome structural variation.

This motivated us to elaborate three strategies of genome evolution (shrinkage, expansion, and stasis) between which organisms may switch under the influence of stochastic mutations and/or selection pressure.

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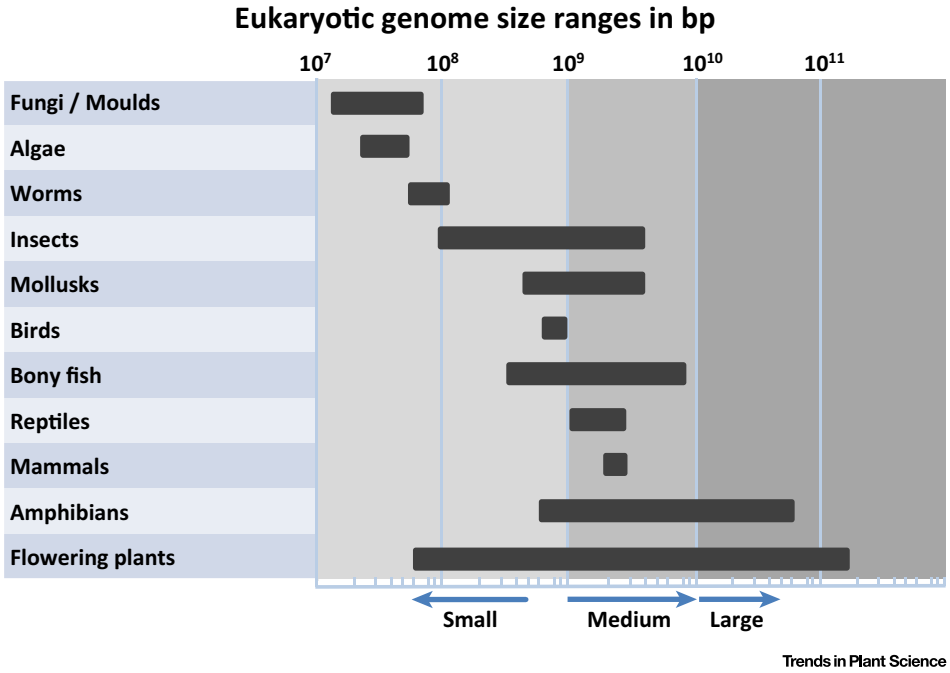

Figure 1. Eukaryotic Genome Size Ranges in Base Pairs. Small to very small (<500 Mbp), very large (>10 Gbp), and medium-sized (1– < 10 Gbp) genomes preferentially follow shrinkage, expansion, and equilibrium strategies, respectively, during genome size evolution. Adapted from Wikipedia.

The main sources of genome structure variability are sex (crossover between homologs, meiotic segregation, and gamete combination), **WGD** (see Glossary), and DNA DSB misrepair *sensu lato*, which includes amplification of retroelements (Figure 2).

Inspired by our work on genome evolution in the plant genus ***Genlisea***, we attempt to link the observed mechanisms and constraints of genome evolution. In the following six sections we present, and argue in favor of, six theses.

Deletion-Biased DNA DSB Repair is the Main Reason for Genome Size Reduction

Genome size reduction occurs when the balance between loss and gain of sequences is shifted toward a decrease of net nuclear DNA content. DSBs are a ubiquitous, frequent, and hazardous type of DNA damage. They can be caused directly – for instance, by endonucleases or ionizing radiation – or indirectly via interference of single-strand breaks (which arise during excision repair of DNA damage other than DSBs) and DNA replication. The indirect appearance of DBSs was concluded early from the observation that mutagens, which do not induce DSBs directly, need to be present during S phase to cause chromosome rearrangements, while DSB-inducing agents cause structural chromosome mutations in all cell cycle phases (for a review see [8]). Unrepaired DSBs are lethal for dividing cells because they result in loss of acentric fragments and in terminal instability of centric fragments (due to the lack of a protective telomere) of monocentric chromosomes. Several pathways have evolved for DSB repair, all of which can work either error free or error prone (Figure 2) (for reviews see [9–11]). Erroneous DSB repair generates various types of mutations that, if viable, contribute to genetic variability. Even (retro)transposition is a matter of DSB repair *sensu lato* [12]. While transposon excision employs the host cell's enzyme machinery for DSB repair to seal the break, insertion of mobile elements mostly utilizes transposon-inherited machinery. Mobile element insertion itself represents a mutation in addition to regular target-site duplication.

Glossary

Dysploidy: nearly euploid alteration of chromosome number (for a review see [22]). Reduction of chromosome number can be achieved during 'fusion–fission cycles' when telocentric chromosomes experience a translocation with breakpoints at their centric ends (Figure 3A). Another mode of reduction of the chromosome number results mainly from reciprocal translocation with breakpoints within or close to the centromere in one chromosome and within or close to the telomere in the other (Figure 3B,C). Such processes yield a 'compound' chromosome [50] that combines two original heterologous chromosomes (corresponding to two linkage groups) into one and mimic 'end-to-end' or 'nested' chromosome fusion as illustrated in Figure 3B and C, respectively. However, because telomeres prevent direct fusion, and often one original chromosome's centromere is lacking, reciprocal translocation and subsequent loss of the (sometimes submicroscopically) small second translocation product is the more likely scenario.

***Genlisea*:** carnivorous plant genus of the Lentibulariaceae family displaying a 25-fold range of genome size between its species, with some genomes much smaller than that of *Arabidopsis thaliana* [51]. Two *Genlisea* species with an 18-fold genome size difference have been sequenced as a model to study the reasons for and consequences of genome evolution yielding large genome size differences [18,27,52].

Whole-genome duplication (WGD): can be based on duplication of one genome yielding two identical copies (autopolyploidy) by skipping of mitosis between two somatic replication cycles or via formation of a restitution nucleus during meiotic division. Alternatively, WGD can result in allopolyploidy, combining related but not identical genomes, by fusion of unreduced gametes of different species or by fusion of reduced gametes and subsequent chromosome doubling. In contrast to alloploidy, autoploidy can cause karyotypic instability (and, after some generations, return to diploidy) due to irregular meiotic multivalent formation between homologous chromosomes. However, even autoploid lineages can be meiotically stable when based