

EDITORIAL: REFLECTIONS ON *THE PLANT CELL CLASSICS*Genomic Balance Plays Out in Evolution^[OPEN]

I will never forget the “Ah-ha” moment I had upon reviewing the article by **Blanc and Wolfe (2004)** at the beginning of my stint as a coeditor of *The Plant Cell*. In the few years preceding that submission, it had become increasingly known from genome sequences that many species had evidence of whole genome duplications (WGD) in their evolutionary history. In *Arabidopsis* (*Arabidopsis thaliana*), there was evidence for at least three successive WGDs. Genes were present in duplicate in syntenic arrangements, indicating that the two copies were not the result of local multiplication. Most genes, however, had returned to a singleton state to produce a near diploid gene repertoire. The contribution of Blanc and Wolfe was that the retained genes were not random in terms of their functions. As a general rule, transcription factors and signal transduction components were overrepresented among the duplicates present.

Our laboratory had a longstanding interest in dosage sensitivity dating from the finding that changes in the copy number of parts of genomes (aneuploidy) had a greater modulation of gene expression than changing the whole set of chromosomes (ploidy; Birchler and Veitia, 2007), suggesting that the stoichiometry of the genome had an impact on gene expression and quantitative characteristics (Birchler et al., 2001). Over the years, we had sought single genes in *Drosophila* that might mimic the effects of aneuploidy giving inverse or positive correlative dosage modulations of gene expression across the genome. When the collection of these dosage-sensitive modifiers was summarized, the functions of these genes were various transcription factors and signal transduction components (Birchler et al., 2001). Thus, there was a parallel between the classes of genes that were dosage sensitive on gene expression and the phenotype and those that were preferentially retained following WGD. Blanc and Wolfe noted this parallel.

Others in the field of evolutionary genomics came to a similar conclusion about the classes of genes that were retained following WGD (Freeling, 2009). If the parallels to the aneuploidy/ploidy comparisons held, then there would be a complementary underrepresentation of the types of genes that were retained after WGD. In other words, if deletion of dosage-sensitive genes was detrimental following WGD and selected against, then small-scale duplications of the same classes of genes would also be detrimental, in analogy to the behavior of plant aneuploids (Birchler and Veitia, 2007). This predication was in fact supported. A comprehensive analysis of retained genes following WGD and comparisons with representation in small-scale duplications from sequence data across angiosperms reveal the generality of dosage balance sensitivity (**Tasdighian et al., 2017**).

The field has expanded to examine many aspects of WGD and the parameters of genome fractionation. An interesting

phenomenon discovered from these studies is that of subgenome dominance (Freeling, 2009). When divergent genomes come together to form an allopolyploid, the two subgenomes that result often have different levels of overall expression. This difference is maintained over evolutionary time and can have an impact on genome fractionation. In a study of subgenome dominance in monkeyflower (*Mimulus* spp), a comparison was made of an interspecific hybrid, a newly produced allopolyploid, and a natural allopolyploid to compare this difference (**Edger et al., 2017**). An interplay of transposon density in subgenomes, DNA methylation, and gene expression is implicated in this dominance.

MicroRNAs (miRNAs) are small RNAs that often modulate the levels of transcription factor expression by their impact on target mRNA levels. When the miRNA genes were examined in the grass family, it was found that duplicates were overretained following WGD and that there was a differential fractionation between the subgenomes (**Abrouk et al., 2012**). There is a core retention of miRNAs and their targets, indicating a resistance to differential return to the singleton state and a need to maintain the regulatory balance.

Further elaboration of fractionation involved an examination of the metabolic network of *Arabidopsis* (**Bekaert et al., 2011**). These authors studied the interplay between relative dosage of duplicates and absolute dosage. They note that gene duplication will be maintained for enzymes for which a high copy number is needed to maintain metabolic flux. They identified a difference in flux bias between the two most recent WGDs and discussed how relative versus absolute dosage in the resolution of duplicates occurs following WGD.

The retention of duplicate genes involved in regulatory processes for longer periods of evolutionary time provides the grist for evolutionary innovation (Birchler and Veitia, 2012). While such a contention might appear contradictory given the selection pressure to maintain a balanced dosage, it is clear that new functional balances can emerge (Birchler and Veitia, 2007), as evidenced, for example, by the fact that of the three readily discernible WGDs in the *Arabidopsis* genome, there is a decreasing number of retained genes with receding time from the present. As new functional balances evolve, new morphological innovations can emerge and the duplicate pairs can undergo subfunctionalization or neofunctionalization that will lock their duplicate nature in place going forward.

The role of genomic balance in evolution is an ongoing active area of research. There are many aspects of the role of “balance” in expression (Hou et al., 2018) and evolution that are exciting avenues for future exploration. Understanding the interplay of networks and regulatory cascades and the emergence of new functional balances over time has been little explored to date but will become more accessible with new sequencing technologies. Coupling these data with biochemical studies of the assembly

and interactions of multisubunit regulatory machines is needed to determine the critical steps molecularly at the cellular level that condition the retention of dosage-sensitive duplicates in populations. Intercalating data on global gene expression with population and evolutionary genomics of regulatory genes will help elucidate what stoichiometric relationships impact reproductive fitness to varying degrees. The pages of *The Plant Cell* have included many seminal articles in the establishment of this field and, hopefully, will continue to do so in the future.

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*References highlighted for the 30th Anniversary of *The Plant Cell*.