Genomic Balance and Speciation

James A Birchler[1] and Reiner A Veitia[2]

[1]Division of Biological Sciences, University of Missouri, Columbia, MO, USA. [2]Institut Jacques Monod, Universite Paris Diderot, Paris, France.

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ABSTRACT: The role of genomic balance in accumulating species hybrid incompatibilities is discussed. Aneuploidy has been shown to produce more global modulations than polyploidy with the responsible genes being transcription factors and signaling components involved in molecular complexes, illustrating a stoichiometric component to gene expression. Genomic imbalance is usually detrimental to the organism and in many cases results in lethality. Here, it is proposed that once gene flow is prevented between or within populations by various speciation initiating processes, the stoichiometric relationship of members of macromolecular complexes can change via compensatory drift with the eventual result of newly established functional balances. However, when these new relationships are brought together in interspecific hybrids, detrimental consequences will occur. We suggest that these detrimental interactions contribute to hybrid incompatibilities.

KEYWORDS: Gene balance hypothesis, aneuploidy, polyploidy, hybrid incompatibility, whole genome duplication, dosage sensitivity

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CORRESPONDING AUTHOR: James A Birchler, Division of Biological Sciences, University of Missouri, Columbia, MO 65211, USA. Email: birchlerj@missouri.edu

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When barriers to gene flow emerge in a population or between populations, the path to reproductive isolation is set in motion.[1] Many factors can be in play to foster speciation, both pre- and post-mating, as well as at pre- and post-zygotic stages. Speciation can be initiated by geographic isolation, behavioral preferences, assortative mating of similar or dissimilar genotypes, etc.[1] Once such reproductive separation has begun, there can be a snowball effect via hybrid incompatibilities that reinforce reproductive barriers. Here we will focus on the post-initiation issue of genomic balance and on how it can contribute to enhancing the incompatibility between species.

Genomic imbalance due to gene duplications or deletions as well as from regulatory mismatches in signaling systems or between *cis* and *trans* factors can be detrimental to organismal fertility, the phenotype, and, in severe cases, viability.[2] This is true of even small regions of the genome. Indeed, the aneuploid effects can be reduced to the action of single genes.[3] These genes include transcription factors and signal transduction components that are typically dosage sensitive to varying degrees on the phenotype. Increasing aneuploidy within a species causes greater detrimental effects indicating that there is some degree of additivity. These effects result from changing the quantitative expression of a ratcheting number of regulatory genes. Here, we argue that, because imbalanced genomes within a species can be detrimental or even lethal, then diverged regulatory balances between related species could contribute to hybrid incompatibility. We discuss evolutionary genomics evidence that indicates such balanced interactions can shift over time and therefore contribute to hybrid incompatibilities.

Hou et al[4] examined the effects of imbalance in Arabidopsis, yeast, and murine data, similarly to previous studies in Drosophila.[5] In Arabidopsis, examination of a set of 5 trisomic chromosomes and of a ploidy series of diploid, triploid, and tetraploid genomes showed a progressive increase of overall transcriptome size, but with few relative changes in the ploidy series. However, with each of the 5 trisomic genotypes studied, global gene expression was much more disrupted, with the most common effect being a dominant negative inverse effect. Comparison of transcription factors and their predicted targets in expression networks revealed considerable discordance between the 2 data sets, indicating that genomic (and thus transcription factor-target) stoichiometry plays an important role in quantitative gene expression. Although there is a complicated relationship between overall gene expression and the phenotype, global modulations are likely to be the underlying basis of the organismal effects.[2,3]

Balance considerations play out in evolutionary and population genomics.[6] Most taxonomic groups of eukaryotes have experienced whole genome duplications (WGDs) in multiple iterations. Such WGDs become fractionated via extensive deletions toward a diploid state, but genes encoding members of multi-subunit complexes are preferentially retained for longer periods. These include regulatory molecules such as transcription factors and signal transduction components. This fact illustrates a constraint on their stoichiometry enforced by reduced evolutionary fitness if the relative concentrations are changed by single gene deletion or duplication of 1 member of an interacting group. The complementary result is that genes encoding members of multi-subunit complexes are underrepresented in small-scale duplications,[7] again indicating a detrimental effect if the stoichiometry is upset.

Nevertheless, the fractionation of WGDs continues even for members of complexes, albeit more slowly, as indicated by the repeated observation that the number of remaining duplicate gene pairs eventually declines with time.[6] This fact

illustrates that new functional balances emerge when contrasted with the under-representation of interacting duplicates in populations and the detrimental effects of experimental aneuploids.

The narrow range of tolerance of regulatory imbalance suggests that the magnitude of variation within a population is constrained. Accordingly, interacting proteins display similar levels of expression variation and their levels are positively correlated across strains in fruit fly and yeast.[8] Although it is thought that small quantitative effects can be tolerated, especially for peripheral subunits of multimeric complexes,[9] even small decreases in the expression of such subunits, if they are represented *n* times within the complex, are amplified to the power of *n*.[10] As variants in peripheral components accumulate over evolutionary time, the impact of other dosage-sensitive bridge subunits can evolve accordingly. Because any one regulatory complex has many components and their own expression is the result of a regulatory cascade, the number of combinations of subtle regulatory variants that can impact a phenotype is astronomical, providing many paths to evolve depending on the nature and strength of selection. Thus, although regulatory balance is critical under any one set of stoichiometries, they can evolve to different functional relationships over time.

Thompson et al[11] have modeled how duplicated genes can evolve while under dosage balance selection in a "compensatory drift" model. In this model, dosage balance selection constrains the total expression from the 2 members of the duplicate pair but allowing each to change. Although the expression of the individual copies can evolve, they are nevertheless held in duplicate following a WGD because dosage balance overall is not disrupted. An interesting topic for further modeling would involve how interacting duplicate pairs, each held by compensatory drift, eventually find a "new" balance with the joining of different variants in a population. Such considerations can explain how duplicate pairs are retained for longer periods than most genes but eventually become fractionated to singletons while still exhibiting a balance relationship.

There is experimental evidence that regulatory divergence can evolve between related species.[12] As an example, this study found that 78% of expressed genes were divergent between 2 Drosophila species, *melanogaster* and *sechellia*, which are nevertheless sufficiently related such that successful hybrids can be produced. Analysis of *cis* and *trans* regulatory variation in hybrids indicated a fairly large contribution of the latter. The *cis* regulatory variants were additive as might be expected from changes of the associated regulatory motifs of target genes. *Trans* variants are generally considered to exert regulatory effects across the genome. Despite their prevalence, their behavior is generally nonadditive illustrating epistatic interactions that have evolved between the 2 related species.

In an example of the determination of hybrid incompatibility loci in tomato, segments of an undomesticated species placed into *Solanum lycopersicum*, when examined in hybrids, illustrated the accumulation of hybrid incompatibilities. Quantitative trait loci were examined for pollen sterility and seed sterility incompatibilities.[13] Seed sterility factors seem to accumulate faster than expected, illustrating a snowball effect of incompatibilities. The pollen sterility incompatibilities, on the other hand, showed antagonistic interactions that did not accumulate rapidly.[14] The basis of this difference is unknown but multiple incompatibility loci were documented in related species for both traits illustrating their accumulation.

In a study of Drosophila,[15] portions of the *melanogaster* X chromosome carried on the Y chromosome were introduced into species hybrids of *melanogaster/santomea* (*mel/san*), *melanogaster/simulans*, and *melanogaster/mauritiana*. Numerous segments caused a dominant lethal condition in males in hybrids but not in intraspecific crosses. More such effects were found for the more evolutionarily divergent combination *mel/san*, suggesting a greater accumulation of incompatible variants. These experiments involve duplication of the added region raising the possibility that they result from aneuploid lethality. However, they are not lethal in *melanogaster* as duplicate segments, indicating that any dosage impact (as opposed to a merely completely dominant one) they have is more severe in the hybrid males. There is little impact in females, but dosage compensation of the male X chromosome would predict a higher expression of a duplicate in males than a triplication in females, which might account for this difference.

These examples illustrate the accumulation of numerous variants that condition incompatibility in hybrids between related species. The molecular basis of these variants is presently unknown. An interesting area of investigation in the future might be to examine their relationship to dosage-sensitive regulatory factors and whether altered stoichiometries among them could account, at least in part, for the incompatibilities.

In summary, genomic imbalance affects the phenotype as evidenced by the contrasting effects of aneuploidy and polyploidy.[2,3] Global patterns of gene expression are modulated by regulatory imbalance.[4] Duplicate genes have different trajectories of evolution depending on whether they are doubled via WGD or in small segments suggesting an impact of stoichiometry.[6,7] Dosage-sensitive regulatory genes contribute to quantitative trait genetics in that highly multigenic control occurs with each gene contributing a small effect. There is a constraint on the magnitude of tolerated variation at such loci.[2,3] Collectively, these principles suggest that genome balance could potentially play a role in the accumulation of incompatibility loci after the initiation of the speciation process. The modeling of compensatory drift[11] illustrates how this could occur and the evolutionary genomics of genome fractionation following WGD suggest that new balances evolve.[6,7] The long history of experimental observations that genomic imbalance can be highly detrimental lays the foundation for the idea that bringing together in a new combination diverged regulatory

interactions that upset functional stoichiometries could be detrimental as well, which might be reflected in the hybrid incompatibilities.

Author Contributions

JAB and RAV wrote the paper.

ORCID iD

James A Birchler https://orcid.org/0000-0003-3643-2756

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