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Review

Kinetics genetics: Incorporating the concept of genomic balance into an understanding of quantitative traits

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ABSTRACT

While most mutations are recessive, variants that affect quantitative traits are largely semi-dominant in their action making hybrids between divergent genotypes intermediate. In parallel, changes in chromosomal dosage (aneuploidy) for multiple regions of the genome modulate quantitative characters. We have previously argued that these observations are a reflection of a common process, originating from the more or less subtle effects of changes in dosage on the action of multi-subunit regulatory machineries. Kinetic analyses that vary the amount of one subunit of a complex while holding others constant do not always predict a linear response for the production of the whole. Indeed, in many instances, strong non-linear effects are expected. Here, we advocate that these kinetic observations and predictions should be incorporated into quantitative genetics thought.

Contents

1. Introduction

Both Mendel [1] and Darwin [2] noted the common observation that hybrids between organisms with different phenotypes of domesticated plants and animals were more or less intermediate between the two parents. Indeed, once the field of quantitative genetics came into being, this fact became a major tenet of the field. When the underlying genetic basis was understood,at least in terms of numbers of genes, it was clear that the many loci affecting any one trait show intermediate contributions to the overall effect [3]. Ironically, the factors chosen by Mendel for in depth study exhibit no such behavior but instead show an all or none response in the hybrid between different parents, which is referred to as dominant or recessive. Indeed, once induced mutations could be made in plants, it was clear that this all or none behavior was the most common effect of mutations [4,5]. While there is no doubt that there is a

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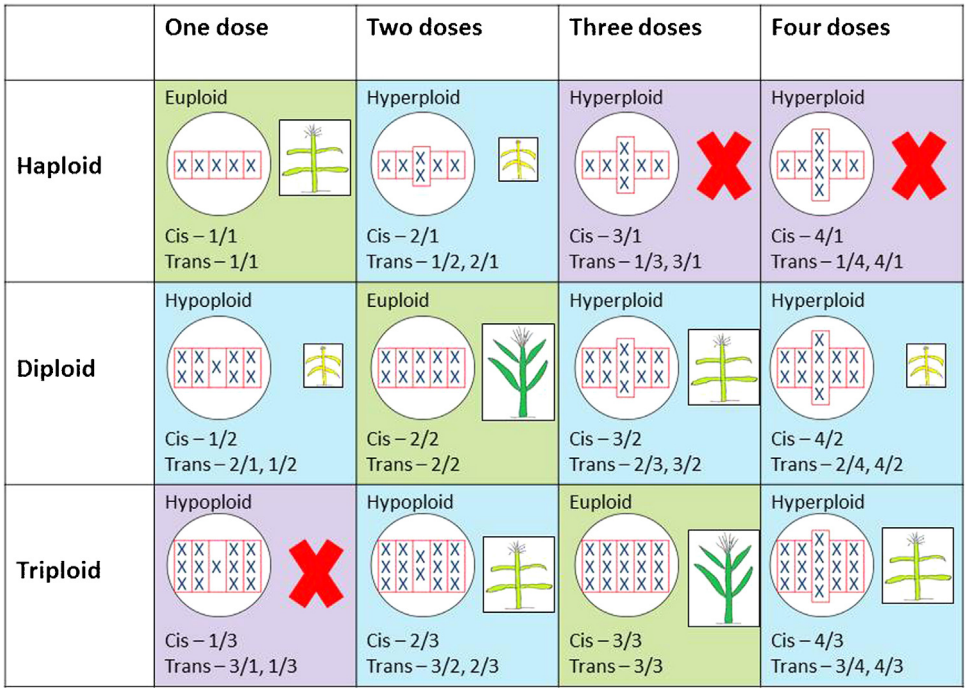

Fig. 1. The aneuploidy/ploidy level impact on phenotype. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Rows represent ploidy level, in a range including haploid (1n), diploid (2n), and triploid (3n). Columns represent the dosage level of a single chromosome selected from the complete set, in a range from one to four copies. Each cell includes an illustration of the chromosome complement; a label for the dosage relationship presented (hypoploid, euploid, or hyperploid); ratios of cis and trans effects, which may occur under the given dosage conditions; and an illustration of the generalized representative phenotype of a plant with the given chromosome complement. The cis effects represent the change in dosage of the chromosome of focus. The trans effects represent the direct and inverse effects on global gene expression that are most typically found in aneuploids. A red X indicates a dosage condition that is likely to be inviable. The wild-type chromosome complement of this idealized plant is 2n = 10.

gradation of phenotypic impact of various mutations, this apparent loose dichotomy between the basis of qualitative and quantitative characteristics is explored with specific reference to the concept of genomic balance that emerged from studies of copy number changes of individual chromosomes versus whole genomes (Fig. 1).

The idea of genomic balance initially grew from work on *Datura* [6,7]. Altered phenotypes were attributed to additional chromosomes in this once popular genetic model species. Eventually, an extra chromosome (i.e. trisomy) was found for each of the twelve pairs in the karyotype and each caused a distinctive spectrum of changes to the phenotype. A different set, called secondary trisomics, was produced in which each chromosome arm in the karyotype was individually duplicated, thus adding two copies of all of the genes on that chromosome arm to the respective genotype. These usually produced greater phenotypic effects because of the increased dosage. Each of the 24 chromosome arms was distinctive in the type of dosage effect revealed. Subsequently, changes in the copy number of the whole genome of *Datura* were produced, i.e. a ploidy series [7]. Each ploidy had its characteristic phenotype but what became apparent was that changing whole sets of chromosomes had less effect than changing only a portion of the genome. These results were recapitulated in many other species of eukaryotes. In maize, it is possible not only to add chromosomal segments but also remove them. Both additions and subtractions from the genome reduce the height of such plants [8–11]. A recent collection of fine scale heterozygous deletions in Populus, which can be recovered and maintained by vegetative propagation, also illustrates the impact of gene dosage on phenotype [12].

Furthermore, the detrimental effects that aneuploidy has on the phenotype depends on the level of ploidy in which it occurs. Disomic haploid plants having a duplicated chromosome on a haploid background of *Datura* or maize are highly defective and much more affected than the corresponding trisomic in an otherwise diploid [13,14]. Monosomics of hexaploid wheat that are missing one chromosome are reasonably healthy and even nullisomics that would basically remove 1/3 of the copies of relevant homoeologous chromosomes are viable [15]. These observations support the conclusion that the relative difference or stoichiometry of the genomic parts (and thus of the encoded gene products) has an impact on the phenotype.

The differing behavior of aneuploidy and polyploidy on phenotypic characteristics led to the concept of genomic balance. The interpretation afforded to these results grew into the idea that the varied chromosome produced a gene dosage effect for the genes encoded therein and that the relative amounts of gene-products compared to those encoded by the remainder of the genome were detrimental. This interpretation in its simplest form has persisted to some degree to the present. As we will note below, the situation is clearly more complex, with an involvement of the interaction of regulatory molecules and their global impact on the target genes.

Parallels between the genetic control of quantitative traits and the impact of aneuploidy have been previously noted [16]. With quantitative traits, multiple genes with intermediate effects are involved with any particular phenotypic characteristic. In other words, a dosage effect in the hybrid occurs between the parental extreme phenotypes. With aneuploidy, multiple chromosomal regions will have a dosage impact on the same phenotypic characteristic. It thus seemed reasonable that the aneuploid effects were grounded in the same underlying basis as the control of quantitative traits. Indeed, multiple aneuploidy effects were documented for a single eye color phenotype in *Drosophila* [17].

Subsequently, analogous types of effects on gene expression were found for the difference between aneuploidy and ploidy [16,18–23]. In other words, aneuploidy modulates gene expres-