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Review

Aneuploidy in plants and flies: The origin of studies of genomic imbalance

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ABSTRACT

The early principles of the impact of aneuploidy were determined in plants and *Drosophila*. Here we summarize the classical results and then relate them to more current studies of gene expression in these taxa. As a general rule, aneuploidy is detrimental, even to the point of lethality, compared to changes in the dosage of the whole genome. Gene expression studies demonstrate an analogous relationship, namely that changes in dosage of chromosomes or chromosomal segments will modulate many genes but changes in whole ploidy have much less of an effect. One of the most common trans-acting effects is an inverse response of a gene to the altered dosage of a chromosomal segment. This effect can produce dosage compensation when it occurs for a gene that is also present in the varied region. Some open questions in the field of aneuploidy research are discussed.

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1. Introduction

The realization of the existence of aneuploidy came from studies of *Drosophila* and *Datura* in the early days of the field of genetics. The description of nondisjunction by Calvin Bridges in the first article in the journal Genetics noted that individuals could have changes in chromosome number and was confirmatory of the chromosome theory of inheritance [1]. These cases involved the sex chromosomes of *Drosophila* and thus did not produce any abnormal phenotypes because the Y chromosome in flies is highly degenerate or the change in dose of the X chromosome changes the sex of the flies. Studies in the flowering plant *Datura* led to the discovery that additional chromosomes in this species would cause an altered phenotype [2]. This work by Alfred Blakeslee and colleagues expanded over the years to define many of the initial parameters of aneuploid syndromes.

There are twelve chromosomes in *Datura* and eventually Blakeslee and colleagues recovered a trisomic for all of these chromosomes [3]. Compared to the progenitor line, each had a characteristic phenotype that allowed it to be distinguished from normal. In particular, the seedpods were used for this classification. These findings made it obvious that each chromosome had a dosage effect that could modify the phenotype in a certain way but that these effects overlapped.

When extra chromosomes are present in plant species, the extra centromere present can undergo a phenomenon of centromere misdivision. This type of event has been observed in meiosis as the attachment of a centromere from both poles with a subsequent fission into two functional parts. Thus, from the primary trisomics found in *Datura*, these stocks would throw off individuals that exhibited a portion of the characteristics typical of the primary trisomics. When examined cytologically, these plants carried a mirror image chromosome of one arm of the trisomic

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chromosome, which is referred to as an isochromosome. When present as an extra chromosome, the individuals are referred to as a secondary trisome [3]. The presumed origin of these chromosomes is that centromere misdivision occurred and the broken end fuses upon itself after replication. Twenty-four secondary trisomics were recovered in *Datura* representing the complete collection of isochromosomes of all arms. As noted, each of these subdivided the phenotypic characteristics of the primary trisomics but the effects were often more severe for the aspects involved.

In parallel with the aneuploid studies, the Blakeslee group also produced an extensive ploidy series in *Datura* involving monoploid, diploid, triploid, tetraploid and higher levels, some of which as sectors on plants [3]. The ploidy series also have characteristics specific to each level but the observation of note is that the aneuploid effects are in general more severe than a comparable step in dosage of the whole genome. In other words, for example, a secondary trisomic as an extra chromosome supplies four copies of a particular chromosome arm. They typically have a much more detrimental effect on the phenotype than a tetraploid that has four copies of the whole genome. Indeed, when an isochromosome is present as an extra chromosome in anotherwise haploid, the plants are severely defective [4]. This principle is illustrated in Fig. 1.

Returning to *Drosophila*, Bridges recovered a triploid female and studied her progeny [5–8]. They produced triploid and diploid females among other genotypes. These females gave rise to individuals with different copies of the X chromosome, which were recognized as triploid intersexes and rarely triploid metamales with one X chromosome together with various diploid genotypes [5]. What was revealed from these studies was that certain aneuploids were missing. Specifically, there were no trisomic flies for chromosomes 2 and 3. Various doses of the diminutive 4th chromosome were present. Thus, in *Drosophila* as in *Datura*, increasing the dosage of the whole genome to three copies produced a viable genotype but three copies of individual chromosomes was highly detrimental, in this case, lethal.

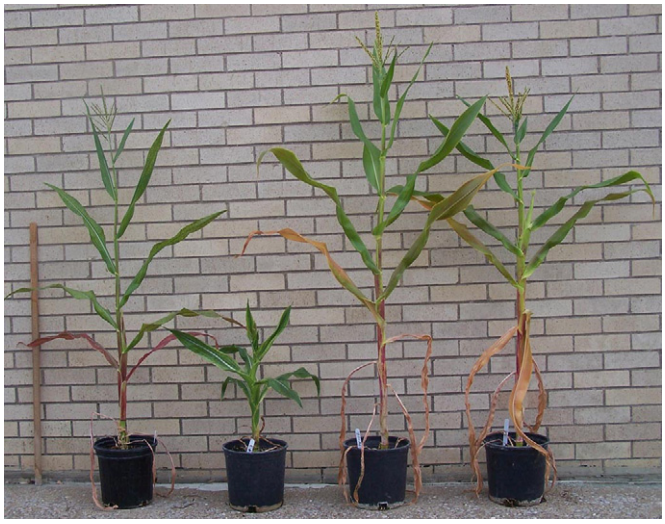

Fig. 1. Illustration of genomic balance on phenotypic characteristics in maize. The depicted plants are from the left to right, haploid, haploid plus an extra short arm of chromosome 5, normal diploid and diploid with an extra short arm of chromosome 5. All plants are in a related genetic background. The comparison illustrates that adding a part of the genome has a much more detrimental effect than a whole genome change. For examples, the haploid plus a chromosome arm is highly defective with its two copies of that arm. However, by changing the whole genome from one copy in the haploid to two copies in the diploid has a straightforward type of phenotypic change. Also illustrated is the fact that adding an extra copy of a chromosome arm to the diploid has a detrimental effect but not nearly as much as adding the same segment to a haploid plant. Collectively, the comparison illustrates the concept of genomic balance.

From these early studies, the *Datura* and *Drosophila* data formed a coherent picture that altering the dosage of a part of the genome had a much more detrimental effect on the organism than changing the dosage of the whole genome. This concept materialized into the ill-defined idea of "genomic balance". It has permeated into genetic thought as a vague idea that does not address the molecular basis for these effects. However, we will return to this subject below.

2. Dividing chromosomes for fine scale studies of aneuploidy

The ability to divide the genome into smaller and smaller regions that could be tested for their effects was facilitated by the work of Patterson and colleagues [9] with the induction of translocations between the small 4th chromosome and either the X or the large autosomes, chromosomes 2 and 3. However, a definitive work on aneuploidy in flies is that of Lindsley et al. published in 1972 [10]. This group produced a large collection of translocations between a marked Y chromosome and the two major autosomes. By making crosses between pairs of translocations with nearby breakpoints, deficiencies and duplications could be produced for the region between the breakpoints of the translocation pair. Using this approach, a systematic analysis proceeding along the length of the two autosomes was conducted. By choosing translocations with more closely positioned breakpoints, more refined segments could be studied. Merriam produced a set of X; Y translocations that could dissect the X chromosome [11].

Some generalities that emerged from this work include the fact that trisomic regions are less detrimental than comparable monosomics. Moreover, only a few regions of the genome were found to be haplo-inviable, i.e. lethal when only one instead of two copies of the region is present. One site was found to be triplo-lethal (and was also haplo-lethal). Nevertheless, as the size of the monosomic region increased, the probability of lethality increased. Also, although few haplo-lethal regions were identified, many regions were haplo-abnormal in that there was a recognizable effect on the phenotype from the monosomic state.

Within the plant kingdom the analysis of monosomics in otherwise diploid individuals is restricted to maize. The utility of maize for aneuploid studies derives from the presence in the species of an unusual "dead" chromosome, the supernumerary B chromosome. This chromosome is neither required nor detrimental at low copy number. Its dispensability is countered by an accumulation mechanism that involves nondisjunction at the mitosis that makes the two sperm and then preferential fertilization of the egg as opposed to the polar nuclei by the sperm carrying the B chromosomes in the process of double fertilization in plants. When translocations are produced between the B chromosome and any of the normal 10 chromosomes, then the attached normal or "A" chromosomal segment follows the behavior of the B centromere [12]. Thus, gametes can be produced that have zero or two copies of the A chromosomal segment. Because nondisjunction does not happen at 100% of the time, there are also some cases in which both sperm have a single copy. Thus, after pollination by a B–A translocation stock as a male parent, there can be 1, 2 or 3 copies of the translocated chromosomal segment present. Those with only one copy of the segment are partial monosomics; those with two copies are diploid; those with three copies are partial trisomics. B–A translocations were first induced in the 1940s and the phenotypic characteristics of dosage series of selected regions of the genome were described. A comprehensive phenotypic study of corresponding monosomics and trisomics was conducted by Lee et al. [13]. The generalizations from these studies are that monosomics are usually weaker than