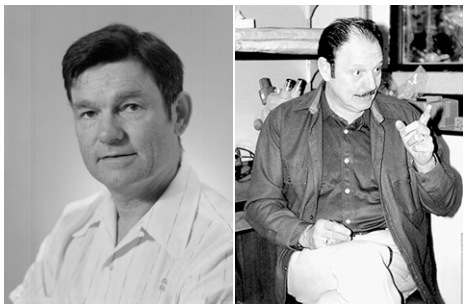
Lindsley and Sandler *et al.* on Gene Dosage and the *Drosophila* Genome



Mariana F. Wolfner[1]
Department of Molecular Biology and Genetics, Cornell University, Ithaca, New York 14853

ORIGINAL CITATION

Segmental Aneuploidy and the Genetic Gross Structure of the *Drosophila* Genome
Dan L. Lindsley, L. Sandler, Bruce S. Baker, Adelaide T. C. Carpenter, R. E. Denell *et al.*
GENETICS March 1, 1972 **71:** 157–184

Lindsley and Sandler *et al.* is, arguably, the first *Drosophila* functional genomics article; it even has "genome" in its title. The authors generated flies duplicated or deleted for specific, mapped regions across the major autosomes by making and combining Y:autosome translocations with defined breakpoints. By examining the phenotypic effects of having precisely the same chromosomal region present in either one or three copies in a diploid fly, the authors identified regions carrying genes required in exactly two copies. This work provided the first genome-wide survey of gene dosage, generated crucial tools and resources, and foreshadowed the collaborative "jamborees" to annotate the fly genome sequence.

Lindsley and Sandler *et al.* used X irradiation to generate chromosome breaks, from which they recovered Y:2 and Y:3 translocations. They used a Y chromosome whose ends carried visible and quantifiable markers (for body color or eye shape). This allowed unambiguous detection of each half of the translocation. The authors determined the autosomal breakpoint of each translocation cytologically, relative to the original *Drosophila* "genome map": the characteristic pattern of polytene chromosome bands. They then selected a set of Y-to-autosome translocations [T(Y:A)] whose autosomal breakpoints fell in a roughly even distribution along the chromosomes. These covered 85% of the two major autosomes, giving breakpoints every ~1/40th of a chromosome.

After establishing stocks of each T(Y:A) over a nontranslocated balancer chromosome, the authors crossed pairs of translocations together. Each cross's progeny included flies with the proximal half of one translocation and the distal half of the other. For each pair of translocations, such progeny either were heterozygous for a deletion of the region between the breakpoints (thus, had just one copy of the region) or carried a duplication of the same region (thus, had three copies of the region). From the presence and phenotype of those progeny, Lindsley and Sandler *et al.* could determine whether the region contained at least one gene required by a diploid fly in two copies for either viability or major morphological phenotypes. After analyzing >140,000 progeny flies from 555 combinations of translocations, they found only 57 such regions. For 56 of these regions, animals with only one copy were dead, abnormal, or "Minute." Only three regions showed a triploid phenotype. Finding so few regions needed in exactly two copies led to an important conclusion: serious phenotypic disruptions due to aneuploidy for large chromosomal regions primarily result from additive effects of aneuploidy for many genes with small individual dosage effects.

The study used *Drosophila* to elegant advantage. For example, the *Drosophila* Y chromosome is not necessary for male viability. It contains a few genes needed for spermatogenesis, but breaks in these genes can be covered by a normal Y (or by the attached X^Y used in the study), making T(Y:A) males fertile. To aid propagation of the translocations in stocks, the authors used a compound X chromosome; presence of all or part of a Y in an XX female does not impair fertility.

This highly cited article remains relevant today, as we think about gene dosage effects in humans as well as other organisms. It generated and categorized chromosomal aberrations, using them to systematically generate reciprocal duplication and deletions of the autosomes that compose ~80% of the *Drosophila* genome. Combining their data with those of Patterson *et al.* (1935) for the X chromosome and Kelstein (1938) for chromosome 4, Lindsley and Sandler *et al.* generated

doi: 10.1534/genetics.116.188441
Photo of Dan Lindsley (left) is courtesy of himself. Photo of Larry Sandler (right) is courtesy of Kent Golic.
[1]Address for correspondence: Department of Molecular Biology and Genetics, Cornell University, Ithaca, New York 14853. E-mail: mfw5@cornell.edu

a genome-wide view of the importance of gene dosage. Their method and strains also provided tools for mapping recessive mutations or enzyme loci to specific chromosomal regions, facilitating gene identification. The authors also identified and began to localize *Minute* loci, now known to be important in protein translation. They also uncovered important phenomena, including the nonrandom distribution of X-ray-induced breakpoints, transient effects of X irradiation on X–Y nondisjunction, and likely cases of meiotic drive.

Finally, this study was also significant from a sociological perspective. In a sense, this was the first genomics jamboree, foreshadowing later gatherings to annotate the first *Drosophila melanogaster* genome some three decades later. Much of the fly work was accomplished in two intense collaborative sessions of fly pushing. First, the Lindsley group converged on Seattle for a summer to join the Sandler group in creating the translocations (using fly food cooked by Lindsley's children). Over the following winter holiday, the Sandler group descended upon La Jolla, California to join the Lindsley group for the intertranslocation crosses. Each laboratory mapped a share of the translocation breakpoints. Finally, many of the junior authors exploited the rigorous training this research provided when they established their own significant careers in genetics. Such training then spread more broadly, as subsequent generations of geneticists were raised, and even tested, on this classic study.

Acknowledgments

Many thanks to Dan Lindsley, Jim Birchler, and Bill Sullivan for providing very helpful comments and input on this article.

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Communicating editor: C. Gelling