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Wisdom from the Fly

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Arguably, almost all research in *Drosophila* can be considered basic research, yet many of the most essential and fundamental concepts of human genetics were first decoded in the fly. Although the fly genome, which is organized into only 4 chromosomes, is about one twentieth the size of the human genome, it contains roughly the same number of genes, and up to 75% of human disease-related genes have *Drosophila* homologues [1]. The fly was prized for its simplicity and utility even before such compelling homology with humans was apparent. Since Thomas Hunt Morgan began his seminal experiments over a century ago, the *Drosophila* system has revealed countless key mechanisms by which cells function, including the factors that maintain chromatin and the signaling pathways that control cell fate determination and organism development. More recently, the fly has emerged as a critical neurobiological tool and disease model for a range of genetic disorders. Here we present a brief retrospective of *Drosophila* as an indispensable genetic system and discuss some of the many contributions, past and present, of this facile system to human genetics.

Chromatin maintenance and regulation

The control and maintenance of chromatin state is a critical to the function of all cells, and much of our knowledge of how genes are regulated by chromatin came from the discovery of position-effect variegation (PEV) by H. J. Muller in 1930. His observation that the expression of a phenotype could be affected by the placement of a gene within different chromatin contexts led to the identification of many enhancers (E(var)) and suppressors (Su(var)) of variegation via genetic screens in the fly. These proteins are often conserved, such as heterochromatin protein-1 (HP-1), and are responsible for the establishment and maintenance of chromatin states. Furthermore, the discovery of Su(var) and E(var) mutations led to the first models of a balanced chromatin state that relies on both activators and repressors for proper function [2].

Critical clues into how chromatin state is initiated and maintained arrived in the 1960s with the identification of polycomb group proteins (PcG) and trithorax group proteins (TrxG) in *Drosophila*. Discovery began through a series of *Drosophila* mutagenesis screens that identified key regulators of the *Hox* genes, which encode a series of homeotic transcription

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factors required for fly embryo patterning and development. The conserved PcG and TrXG complexes, repressors and activators of chromatin, respectively, are responsible for the precise genetic regulation of the *Hox* genes through deposition of a series of chromatin marks.

While early research into PcGs and TrxGs suggested their role in homeotic gene control in both *Drosophila* and mammalian systems, recent genome-wide studies have revealed that these complexes regulate myriad critical genes throughout the genome in metazoa and some plants [3]. PcGs and TrxGs have complex roles in development, cell differentiation, and cell reprogramming because they establish epigenetic "memory" of heritable chromatin states. It is therefore not surprising that the misregulation of these proteins is implicated in a multitude of human disease conditions, most notably cancers [4, 5]. The *Drosophila* system is also a well-suited model for study of the connection between PcGs, TrxGs and tumorigenesis. For example, *Drosophila* is being used to determine how PcGs target specific oncogenes for regulation during cell fate determination [6].

Signaling pathways in development and disease

Just as Muller observed PEV in *Drosophila* as a curious variegated eye phenotype, John Dexter first characterized mutant "notched" wing phenotypes a hundred years ago, spurring a century of investigation into the underlying signaling pathways. The Notch pathway is highly conserved within metazoa and involves a series of receptors, ligands, and transcription factors important in cell-cell communication and essential for cell fate determination and embryonic development.

Another essential group of signaling pathways was first identified through phenotypic observations of the striking loss of wings or halteres caused by a hypomorphic recessive mutation in the *wingless* gene. The conserved wingless (Wnt) signal transduction pathways are involved in a variety of processes, including vertebrate brain, kidney, limb, and gut development. Components of the highly conserved Bone Morphogenetic Protein (BMP) signaling pathway were also initially identified in *Drosophila*. Early studies into the BMP pathway focused on embryo patterning and development, including the early establishment of patterning along the dorsal-ventral body axis. The BMP pathway, along with the related Activin/TGF-β pathway, is now known not only to induce the formation of bone, but also to affect a multitude of cellular functions in homeostasis and during development.

Misregulation of any of the Notch, Wnt, or BMP/TGF-β pathways is implicated in a wide variety of human genetic diseases and cancers [7, 8]. For example, a single point mutation in a BMP receptor is associated with fibrodysplasia ossificans progressiva, a rare autosomal dominant disorder in which muscle and connective tissue are slowly replaced by bone [8]. This disease is currently being studied in a *Drosophila* model [9]. As we extend our understanding of how the signals transduced by each pathway are regulated, the list of associated human genetic diseases will continue to grow.

Drosophila as an essential neurobiological model

The fly has historically facilitated the identification of critical cellular mechanisms and laid the foundation of human genetics. Yet the utility of *Drosophila* is not limited to developmental cellular biology: the fly has recently emerged as an incredibly useful neurobiological model. *Drosophila* is an attractive system in which to study neurobiology for several key reasons. First, there are significant similarities between the fly and human brains, including the expression of important regulatory genes [10]. Perturbed fly behaviors, the output of altered brain function, are well characterized and easily identified, quantified, and genetically traced. Second, the *Drosophila* genome is less complex than those of mammalian models, partially due to the presence of smaller gene families. The genetic simplicity of the fly allows for the identification of interactions that might be masked by redundancy in more complex vertebrate systems. Finally, the unparalleled extensive genetic toolbox already available in *Drosophila* facilitates and speeds discovery.

Because of the extensive genetic tractability and relevance of the fly, it has already been employed to model countless neurodegenerative diseases, including Parkinson's, Alzheimer's, and Huntington's diseases [11], and amyotrophic lateral sclerosis (ALS) [12]. Further, the creation of fly models for human neurobiological diseases allows for large-scale pharmacological testing and drug discovery [11]. These applications are particularly useful, as they can be prohibitively expensive and lengthy in vertebrate models.

Genetic tools in *Drosophila*

Historically, relatively simple phenotypic observations in *Drosophila* have lead to the discovery of complex and conserved genetic mechanisms. The fly will doubtlessly continue to be an indispensable tool for genetic research, especially given that most recently discovered genetic tools are easily modified to work in the fly; RNA interference for transcript knock down, and TALEN and CRISPR tools for gene knock out were all quickly adapted for use in *Drosophila*. These newer tools, coupled with the power of the classical high throughput genetic screen, a relatively simple approach in *Drosophila*, serve to keep the fly highly relevant to the study of human genetics. Additionally, the simplicity of the fly genome compared to complex vertebrate genomes and the large amount of available public data [13] allow for strong computational biology and genome-wide association studies.

In summary, *Drosophila* has historically been an indispensible genetic tool. In addition to numerous other contributions, the fly has revealed mechanistic insights into the conserved processes of chromatin maintenance and signal transduction. It is also apparent that the *Drosophila* system is already a powerful neurobiological tool, and the list of available resources continues to expand at a rapid pace [14]. It is highly likely that future discoveries in the fly will prove to be just as essential to our understanding of human genetics as those early observations of curious phenotypes.

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Table 1

Classic and pertinent *Drosophila* genetics publications.

1914	**John S. Dexter** "The analysis of a case of continuous variation in *Drosophila* by a study of its linkage relations," *American Naturalist*. Included a description of the mutant "notched" phenotype. Morgan later identified the alleles in 1917.
1915	**Thomas Hunt Morgan** *Mechanisms of Mendelian Heredity* Demonstrated the principles of "coupling" and "repulsion," later referred to as "linkage
1925	**Thomas Hunt Morgan** Nobel prize in physiology or medicine awarded in 1933 for discovering the role of chromosomes in heredity. *The Theory of the Gene* Confirmed Mendel's theory of heredity and established the chromosome as the unit of heredity.
1930	**Herman J. Muller** Nobel prize in physiology or medicine awarded in 1946 for production of mutations by X-rays. "Types of visible variations induced by X-rays in *Drosophila*," *Journal of Genetics*. "The frequency of translocations produced by X-rays in *Drosophila*," *Genetics*. Described early observations of position effect variegation (PEV).
1978	**Edward B. Lewis** Nobel prize in physiology or medicine awarded in 1995 for discoveries concerning genetic control of early embryonic development. "A gene complex controlling segmentation in *Drosophila*," *Nature*. A review, summarizing decades of research, in which Lewis presents his view of the bithorax complex and describes Polycomb as a possible repressor.