The Humanized Fly

The complete genome sequence of *Drosophila melanogaster* will be a powerful tool for using fly biology to study human medicine

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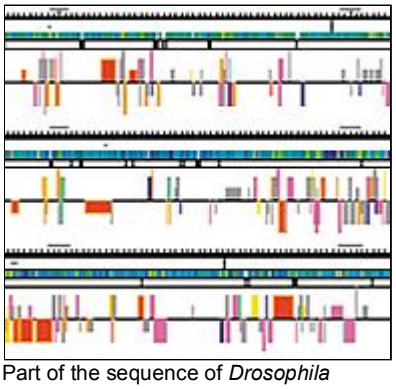
featured article

The fruit fly, which for reasons of its own likes to hover around bananas whenever it has the chance, has been one of the central players in genetics since the early 1900s when Thomas Hunt Morgan's fruit fly studies linked chromosomes to heredity and Herman J. Muller learned that radiation can induce mutations in those chromosomes. Since then *Drosophila* researchers (there are about 6,000 of them today or roughly one for every two known genes) have discovered striking similarities between fruit flies and people.


Part of the sequence of *Drosophila*

Now, with publication in this week's *Science* of the complete genome sequence of the euchromatin or gene-rich regions of the fly, possibilities for finding and exploiting knowledge about the ways in which flies and human beings are biologically alike seem endless. Prior to completion of the genome sequence, estimates of the number of fly genes ranged from 12,000 to 15,000. As of this writing, 13,601 genes have been confirmed but researchers fully expect they will find more as new research gets underway.

Just how alike are fruit flies and people? A handful of examples tell the tale.

Development

Flies breed and reproduce. The expression "breeds like flies" refers to the fact that a single mother fly can have 3,000 babies in the space of a couple weeks. Because the fly genes that determine the shape of a fly's body are similar to human genes, flies are ideal for the study of physical development. Specifically, flies, like people, have "homeobox genes" that regulate the front and back parts of the body and that, when mutated in certain ways, cause predictable anomalies. For instance, flies with a mutated Antennopedia gene grow legs instead of antennae at the top of their heads.

Aging

Flies age and die, faster than human beings, to be sure, but their aging appears to be under the control of similar genes. (*Drosophila's* prodigious reproduction, coupled with their short life span is what makes them ideal or "model organisms" for laboratory research.) Flies have genes for apoptosis, colloquially known as "cell suicide," which is important for maintaining the overall number of cells in the body. A certain amount of apoptosis ensures normal cellular turnover. Flies that carry a mutation in the Methuselah gene live about a third longer than flies that lack this mutation and appear to be better at resisting stress as well.

Cancer

Flies get cancer. Like human beings and other mammals, they have a variety of genes that are known to be important in controlling cell replication and that, when mutated, are

believed to contribute to the development of tumors. Thus, flies, like us, have a p53 gene that may be an ancestor of human p53. *Drosophila* p53 contains some of the same amino acid sequences that appear to be hotspots for mutations in human cancer. In fact, some 67 percent of known human cancer genes have parallel genes in the fly. Interestingly, however, recent studies of the *Drosophila* genome have not turned up any fly genes that parallel the human breast cancer genes, BRCA1 and BRCA2.

Neurons

Recent biomedical research in flies, in other "model organisms" such as inbred mice, and in human subjects, has shed light on the patterns governing the behavior of neurons in the brain. Knowing how and when they fire, and the connections they make or fail to make is vital to understanding neurotransmitters such as glutamate, dopamine (whose dysfunction is central to Parkinson's), and serotonin, that now famous neurotransmitter that contributes to mood and is the basis of antidepressant drugs such as Prozac™ and Zoloft™. Whether fruit flies get depression is something of an unknown, but analysis of *Drosophila* serotonin and other relevant neurotransmitters can be of great importance to drug development and psychiatric medicine.

Parkinson's, Alzheimer's, and other neurological diseases

The number of *Drosophila* genes that correspond to genes associated with human neurodegenerative diseases is quite astonishing. Flies were known to have a gene called "Notch," which is associated with multi-infarct dementia—a kind of dementia that occurs when lots of little blood vessels in the brain burst. They also have a gene similar to the human gene that linked to amyloid plaques in the brains of patients with Alzheimer's disease, and flies have a gene called Presenillin, also associated with Alzheimer's.

New genome studies have uncovered additional *Drosophila* genes that parallel genes for human neurological disease including Tay Sachs disease, which destroys the nervous systems of afflicted children before their third or fourth birthdays, and the gene "tau," which is thought to cause a kind of dementia that occurs in Parkinson's patients. *Drosophila* also have "Parkin," a gene associated with early-onset or juvenile Parkinson's. Flies also get the tremors and loss of motor coordination characteristic of Parkinson's. In a report in this week's *Nature*, Mel B. Feany and Welcome W. Bender of Harvard Medical School report that flies bred with the human gene "alpha-synuclein" show symptoms of brain damage that not only mimic those in humans but also appear to be closer in the fly than those seen in mouse models of Parkinson's. If this observation is substantiated, flies could become an ideal model for testing new anti-Parkinson's therapy quickly and effectively, given the fly's short 60-day lifespan.

Self Defense

Drosophila have gene-based ways of protecting themselves against microbes, using a "pattern recognition" system that, not unlike the human antibody repertoire, is based on killing off invading pathogens that "look" different to the self. *Drosophila* also have genes parallel to the cytochrome P450 family, which encodes proteins that rid the body of foreign or toxic compounds. Analysis of the *Drosophila* genome revealed 90 previously unknown P450 genes, including those that affect the metabolism of drugs such as beta blockers for heart disease, antidepressants, antipsychotics, and codeine—a pain killer and cough suppressant. (No one knows whether a fruit fly can get a cough.)

The Biological Core (or Core Proteome)

The description here of Drosophila genes that parallel those in humans is just a snapshot of the total, which includes numerous genes that play an essential role in all aspects of cell functioning. But one additional point is worth making. There appears to be a small or core number of genes that are essential for life and they all seem to exist in the fly. Human beings

doubtless have more genes than *Drosophila* (approximately 30,000 compared to 13,000) but, as Gerald M. Rubin, head of the Berkeley *Drosophila* Genome Project and lead author of one of the *Science* papers, says, "about 60 percent or more genes are conserved between fly and human." In other words, nature practices the addage against reinventing the wheel. If you've got a core set of genes that work, why not use them over and over again in just subtly different ways. "Complexity does not come from the number of genes but from the way in which they are used," according to Rubin. "Humans may have four copies of a gene where the fly has one, but if you look at the core proteome—the core set of parts—they're not that different. The fly has learning and memory and behavior, it's just not as complex as ours."

His favorite analogy is to supercomputers (such as those needed for genome assembly or worldwide telephone tracking) and desktop PCs. The human is a supercomputer to the PC fly. "It's an organizational issue. The parts are basically the same." And, therefore, it's obvious why the fly is important to us.

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Adams, M.D. *et al*. The genome sequence of *Drosophila melanogaster*. *Science* **287**, 2185-2195 (March 24, 2000).

Myers, E.W. *et al*. A whole-genome assembly of *Drosophila*. *Science* **287**, 2196-2204 (March 24, 2000).

Rubin, G.M. *et al*. Comparative genomics of the eukaryotes. *Science* **287**, 2204-2215 (March 24, 2000).

Feany, M.B. & Bender, W.W. A *Drosophila* model of Parkinson's disease. *Nature* **404**, 394-398 (March 23, 2000).

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