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1980

Mutations affecting segment number and polarity in Drosophila melanogaster have been identified 15 loci which alter the segmental pattern of the larva. These loci probably represent the majority of such genes in Drosophila. Mutations at 15 loci which show homeotic effects do not affect the total number, size, or position of the segments, nor do they point to any other feature which intervenes between the maternal gradient and the formation of the segments.

We have undertaken a systematic search for such mutations, and have identified 15 loci which show novel types of pattern alteration: pattern duplication (segment polarity mutants; six loci), pattern alternations (pair-rule mutants; six loci) and a group of adjacent segments (gap mutants; three loci). The segmental pattern of the normal Drosophila larva

Figure 2 shows the cuticular pattern of a normal larva shortly after hatching. The larval body is divided into three thoracic and eight abdominal segments, each of which is defined by a characteristic set of ridges. The cuticular pattern shows certain morphological features in common. The segmental pattern of the normal Drosophila larva

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In 1980, Christiane Nüsslein-Volhard and Eric Wieschaus published a highly influential paper on the effects of mutations on development of the fruit fly Drosophila melanogaster. This work paved the way for tackling the question of how genes establish the patterns of multicellular organisms and so why, for example, a leg is different from an eye. Subsequent work has shown that many of the principles (and the genes) evident in the fly are common to all animals, including humans.

For most of the twentieth century, Drosophila has been the traditional organism for investigating the genetics of multicellular creatures. Over the years a large number of inheritable variations (mutations) have accumulated in these little flies, consistently revealing themselves as anomalous traits—for example, a curved wing or an unusual eye color. This is the mutant phenotype.

Many such mutants are “viable,” reaching the adult stage, and most studies were based on them. Flies have an external skeleton, the cuticle, which bears a diversity of organs (wings, legs, eyes, and so on) and is largely covered with sensory bristles arranged in characteristic patterns. All of these external structures could be easily inspected with a magnifying glass or a low-power microscope. Inevitably, geneticists were fascinated by the richness in detail of the adult cuticle and the ease of detecting mutations affecting it and the various organs. Classical genetic studies, then, centered on the identification and study of genes involved in the development of adult cuticular structures.

When, during the 1920s, methods were devised to induce mutations artificially, it became clear that although many mutants are viable, many
more are not. The great majority of mutations lead to death of a fly in its embryonic, larval, or pupal stages, so that it never becomes an adult. These mutations were simply labeled as “lethals,” and for a long time they were largely neglected.

From these studies an important class of developmental control agents emerged. These were the homeotic genes, nowadays referred to as Hox genes, which specify the diversity of the body along the axis running from the front of an organism to the back. For example, the adult fly consists of a head, a thorax of three segments, and an abdomen of six (male) or seven (female) segments (fig. 17.1). Each of these segments has its own typical morphology, often referred to as its “identity.” The function of the Hox genes is to determine the developmental programs followed by the groups of cells that make the different segments, so that the appropriate segment identity is formed in each position. Typically, a mutation in a Hox gene transforms the identity of one segment into that of another. For example, in Ultrabithorax mutants the third thoracic segment (which has no wings) develops like the second thoracic segment (which has wings). The mutant fly therefore has two pairs of wings, one in the second and another in the third thoracic segment.

The work of Ed Lewis, at the California Institute of Technology in Pasadena, is especially relevant to our story. Lewis identified and characterized several of the Hox genes that control the manner in which individual segments develop. However, even though the focus of his work was on the adult fly, in 1978 he published a key paper describing for the first time a transformation in larval patterns that resulted when an entire group of adjacent homeotic genes was missing. This genotype was lethal, but Lewis realized that the mutant larvae reached the stage at which the segments had become evident, so he could describe the homeotic transformations based on the larval segment patterns. These larvae showed transformations affect-
ing part of the thorax and the entire abdomen. One reason why this paper was so striking was that it predicted the existence of further Hox genes involved in abdominal development, and these genes were indeed identified some years later.

But the greater significance of Lewis's paper was twofold. It showed that larval patterns were technically easy to study and could serve as well as adult patterns for studying the genetic control of development. But more importantly, it indicated the existence of a process for generating the segments of the body that was independent of the homeotic mechanism. This conclusion stemmed from examination of the mutant larvae: despite the absence of the genes necessary to specify thoracic and abdominal identities, the larvae still had the normal number of segments, although they all developed as thoracic-like segments.

This was the setting for Nüsslein-Volhard and Wieschaus's Nature paper of 1980. They were working at the European Molecular Biology Laboratory in Heidelberg and set themselves the aim of understanding the genetic basis of how the fly's body is initially subdivided into individual segments, and understanding which are the fundamental features of the organization of segments that are common to all of them. To achieve this goal, Nüsslein-Volhard and Wieschaus designed experiments to isolate mutations in all of the genes involved in the formation and disposition of Drosophila segments. Realizing that their aims could not be achieved using adult flies, their assay was based on larval patterns.

The methods they employed were not novel—the approach was a conventional one, with ethyl methane sulfonate being used as the mutagenic agent. But their painstaking strategy was new. Several years of work were involved, as the analysis required thousands of individual matings of flies, and the inspection of the progeny of each mating under the compound microscope. Moreover, as the intention was to identify all of the genes involved in segmentation, it was necessary to complete the experiment to "saturation"—that is, until all or nearly all susceptible genes had been mutated. Saturation usually involves showing that the experiment has produced several mutations per gene, making it unlikely that there are many genes still to be mutated. The task was huge, and meant recording the consequences of some forty thousand matings.

Analysis of the mutations showed that only fifteen genes, an unexpectedly low number, are involved in segmentation. Some in which mutations affected the adult fly were already known, but most had not been identified before. Nüsslein-Volhard and Wieschaus named them for the larval phenotypes that resulted, and for the first time now-famous names such as hedge-
that in a short time all of the segmentation genes concerned were cloned, identified. Drosophila workers were not renowned for their molecular abilities, but that the genes themselves—the specific stretches of DNA—could be identified. The availability of all these mutant flies coincided precisely with the advent of molecular techniques for cloning DNA, meaning that the genes themselves—the specific stretches of DNA—could be identified. The obvious importance of these genes, the straightforwardness of the analysis, and the availability of the mutations triggered general interest in the study of segmentation in the Drosophila community. There was a shift from the study of adults to the study of larvae, whose simplicity of development and well-characterized patterns facilitated further genetic analyses of double- and triple-mutant combinations, and of interactions between genes.

Moreover, the timing of the paper was just right, for it came at a crucial juncture in biology. The availability of all these mutant flies coincided precisely with the advent of molecular techniques for cloning DNA, meaning that the genes themselves—the specific stretches of DNA—could be identified. Drosophila workers were not renowned for their molecular abilities, but suddenly numbers of well-trained molecular biologists from other fields arrived in search of a problem against which to pit their wits. The result was that in a short time all of the segmentation genes concerned were cloned,

*hog, patched, and even-skipped* appeared in print. Moreover, the genes could be subdivided into three well-defined classes known as “gap,” “pair-rule,” and “polarity.” This subdivision was itself of interest, as it suggested steps in the process of segmentation that result in the finer-grained specification of each segment: first, subdivision of large body areas; then the formation of two-segment units; and finally formation of the individual segment units. These have to have a polarity, in which the anterior region that meets the preceding segment is different from a posterior region that lies next to the following segment.

The end of this process is the formation of a chain of segments that are all alike and have a similar organization. The only difference between them is their position along the antero-posterior axis of the body. It is on this scaffold that the *Hox* genes operate; each *Hox* gene becomes active in a characteristic position where it establishes the appropriate segment identity.

The impact of the paper, first on those working with *Drosophila* and later on the whole of biology, cannot be overemphasized. A first consequence was that it made possible the genetic analysis of developmental patterns, which had previously been impossible because nine out of ten mutations are lethal. It turned out that nearly all the lethal mutants live long enough to make larval patterns. At a stroke, then, 90 percent of the *Drosophila* genome was opened up for investigation. In regard to this, as biology becomes ever more competitive, it is worth mentioning Nüsslein-Volhard and Wieschaus’s willingness (very much in the tradition of *Drosophila* genetics) to share their research material: the last sentence of the paper reads “All mutants are available on request.”

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and the molecular analysis of developmental patterns began. As Peter Lawrence has pointed out in *The Making of a Fly*, in 1990 half of the presentations at the main meeting on *Drosophila* development were based on the genes discovered by Nüsslein-Volhard and Wieschaus.

The fusion of developmental genetics with molecular biology has produced one of the most exciting findings in biology: that the basic developmental mechanisms in all animals are much the same. Many of the genes identified by Nüsslein-Volhard and Wieschaus have counterparts in all species, including humans, and also have similar functions. This revelation has dramatically changed the way in which questions in biology are approached and understood; developmental biology has become a general discipline, the principles of which apply to all animals. It has also provided new concepts for understanding the history of life on Earth. Knowledge of how the diversity of body parts is generated during development is a great help in interpreting the differences, generated by evolution, that we see in the ten million or so living species of animals.

Finally, there is also a direct connection with human biology and medicine. Many of the genes described by Nüsslein-Volhard and Wieschaus, or by others who followed their approach, can be directly involved in human ill-health. For instance *hedgehog*, *cubitus interruptus*, *patched*, and *wingless* are all altered in cancer and in other degenerative diseases. The investigations carried out with *Drosophila* will, without doubt, help in the fight against disease.

All in all, Nüsslein-Volhard and Wieschaus's contribution of 1980 was arguably the most influential paper in developmental biology during the second half of the twentieth century. They, together with Lewis, received due acknowledgment of their achievement with the award of the Nobel Prize in Physiology or Medicine in 1995.

**References**


**Further reading**