# Positions, please...

Niall Dillon

Rediscovered in 1900 from the research of Gregor Mendel, and named in 1909 by Wilhelm Johanssen, the gene became one of the most influential scientific concepts of the twentieth century. Yet despite its iconic power, it remains a curiously nebulous entity that defies easy definition. From the start, there was a tension between the concept of the gene as a 'unit of inheritance' — which was defined in purely operational terms as an autonomous unit that transmits specific traits through multiple generations — and the gene as a physical entity — whose position could be mapped in relation to other genes on the chromosome.

The difficulty in reconciling these two views of the gene was highlighted when Alfred H. Sturtevant and Hermann Muller separately described a new type of mutation in *Drosophila* in the 1920s and early 1930s. These mutants were the result of translocations that alter the positions of genes on the chromosome but not their physical structure. For example, placing a gene close to a compacted, transcriptionally silent region (heterochromatin) often gives rise to flies with 'variegated' phenotypes (such as patches of red and white eye colour) where the affected gene is expressed in some cells and silenced in others.

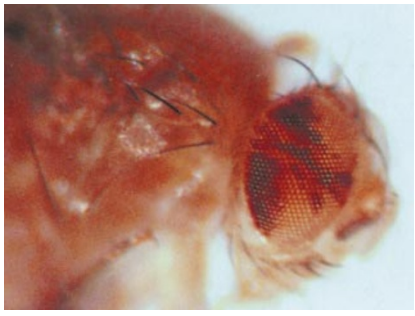
The discovery that genes could be affected by their position on the chromosome raised the question of whether the autonomous gene proposed by classical genetics actually existed. Leslie Dunn commented in 1937 that the gene was showing "signs of disappearing in a cloud of position effects", and Richard Goldschmidt adopted the highly controversial view that the particulate gene concept should be abandoned altogether. The gene was — and still is — too useful to be discarded, but even now, 50 years after the discovery of the double-helical structure of DNA, the problem of the relationship between Johannsen's unit of inheritance and the gene as a physical structure is still not fully resolved.

A gene gives rise to a phenotype through its ability to generate an RNA or protein product. Thus the functional genetic unit must encompass not only the DNA that is transcribed into RNA, but all of the surrounding DNA sequences that regulate RNA transcription. If it is to satisfy the full definition of the particulate gene, the functional unit should also be isolated from neighbouring genes.

Transgenic assays have been used to try to determine the nature of the genetic functional unit and to establish a physical basis for gene autonomy. Because most transgenes are subject to position effects, they can be used to search for sequences that allow them to function normally when integrated at any position on the chromosome. Candidate sequences are introduced into the transgene construct, and expression is analysed to test for sensitivity to integration position. These studies have led to two quite different perspectives on the problem.

The simplest explanation for gene autonomy would be for each gene to be flanked by barriers or insulators that isolate it from surrounding sequences. But despite intensive searches, such barriers have proved to be elusive. Where they have been found, they have turned out to be extremely diverse in structure, and often coincide with sequences that have other functions (for example, gene promoters). This heterogeneity argues against the idea that barrier effects evolved as specific and highly conserved functions. Instead, it suggests that sequences with other roles can sometimes acquire a barrier function by virtue of their location.

There is also a quite different way of looking at genetic functional units, which focuses on the interactions with transcription factors (sequence-specific DNA-binding proteins) that make a gene competent to transcribe its RNA product. If these factors are able to bind to their recognition sites and initiate chromatin remodelling despite the presence of inhibitory chromatin, then they will be able to overcome position effects. Dominance of clustered transcription-factor binding sites over negative position effects was first described by Frank Grosveld and colleagues for the human β-globin locus control region, and has since been demonstrated to operate at a number of other genes. These results portray the functional unit primarily as a dynamic information processor, comprising the transcribed region and associated factor-binding sites, which may extend over hundreds of kilobases of DNA.



**Eye-opener: studies of *Drosophila* showed that a gene's position can affect its function.**

## Gene autonomy

*Position effects continue to raise questions about the physical structure of the particulate mendelian gene.*

Crucially, this type of organization allows functional units to overlap yet still remain isolated from one another if they bind to different sets of factors. As more genes are characterized in detail, it is becoming clear that overlap of genetic functional units is a widespread phenomenon.

Recent studies have also provided intriguing evidence that autonomy might be an optional feature for many genes. Microarray analysis of large numbers of genes in *Drosophila* and *Caenorhabditis elegans* showed that genes with similar patterns of expression are often grouped together on the chromosome — despite being functionally unrelated. The authors of one of these studies, Paul Spellman and Gerald Rubin, have noted that 'leaky' gene expression is often phenotypically silent. They speculate that such expression could be a frequent consequence of being located close to a highly expressed gene. If correct, this would indicate that complete isolation from neighbouring genes — instead of being an intrinsic property — evolves when it is required to prevent harmful position effects.

The particulate gene has shaped thinking in the biological sciences over the past century. But attempts to translate such a complex operational concept into a discrete physical structure with clearly defined boundaries were always likely to be problematic, and now seem doomed to failure. Instead, the gene has become a flexible entity with borders that are defined by a combination of spatial organization and location, the ability to respond specifically to a particular set of cellular signals, and the relationship between expression patterns and the final phenotypic effect. ■

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**FURTHER READING**

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