# THE GENE

*from* GENETICS *to* POSTGENOMICS

Hans-Jörg Rheinberger &
Staffan Müller-Wille

Few concepts played a more important role in twentieth-century life sciences than that of the gene. Yet at this moment, the field of genetics is undergoing radical conceptual transformation, and some scientists are questioning the very usefulness of the concept of the gene, arguing instead for more systemic perspectives.

The time could not be better, therefore, for Hans-Jörg Rheinberger and Staffan Müller-Wille's magisterial history of the concept of the gene. Though the gene has long been the central organizing theme of biology, both conceptually and as an object of study, Rheinberger and Müller-Wille conclude that we have never had a universally accepted, stable definition of it. Rather, the concept has been in continual flux—a state that, they contend, is typical of historically important and productive scientific concepts. It is that very openness to change and manipulation, the authors argue, that made it so useful: its very mutability enabled it to be useful while the technologies and approaches used to study and theorize about it changed dramatically.

"As authors of the definitive history of heredity, Hans-Jörg Rheinberger and Staffan Müller-Wille's account of the gene has been eagerly awaited. It will not disappoint. For anyone who wants to understand the various subtly intertwined meanings of the word 'gene' and where these came from, this is the book to read."

—**John Dupré,** University of Exeter

"*The Gene* is an erudite and elegant history of a [perhaps the] central concept of twentieth-century biology. Rheinberger and Müller-Wille show that the gene's success lay in its plasticity in different experimental registers and its pluralism in connecting divergent theories and scientists. This book is now the definitive synthesis and point of departure for new scholarship."

—**Angela N. H. Creager,** Princeton University

"Rheinberger and Müller-Wille's insightful historical exploration of the many and changing meanings of the gene concept brings much needed clarification to the ongoing debate about the continuing usefulness of the term."

—**Soraya de Chadarevian,** University of California, Los Angeles

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**Hans-Jörg Rheinberger and Staffan Müller-Wille**

*Translated by* ADAM BOSTANCI,

*revised and expanded by the authors*

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*"All concepts in which an entire process*
*is semiotically concentrated defy definition;*
*only something which has no history can*
*be defined."*

— FRIEDRICH NIETZSCHE,
*On the Genealogy of Morality* ([1887] 2007, 53)

## Contents


| | | |
|---|---|---|
| 1 | The Gene: A Concept in Flux | 1 |
| 2 | The Legacy of the Nineteenth Century | 11 |
| 3 | Mendel's Findings | 23 |
| 4 | From Crossing to Mapping: Classical Gene Concepts | 34 |
| 5 | Classical Genetics Stretches Its Limits | 47 |
| 6 | Constructing and Deconstructing the Molecular Gene | 59 |
| 7 | The Toolkit of Gene Technology | 74 |
| 8 | Development and the Evolving Genome | 87 |
| 9 | Postgenomics, Systems Biology, Synthetic Biology | 100 |
| 10 | The Future of the Gene | 112 |
| | Acknowledgments | 121 |
| | Bibliography | 123 |
| | Index of Names | 145 |


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# 1

## The Gene A Concept in Flux

In this book we review a long century of research in biology. Our aim is to present an in-depth analysis of the history of the gene concept, which, in different instantiations, became central to all main branches of the life sciences and promoted unprecedented visions of controlling and directing life. But if the turn from the nineteenth to the twentieth century saw the coming into being of a powerful concept, it experienced an existential crisis a century later. Tracing this history will help us to better understand the changing role of the gene concept in the current age of epigenetics and data-intensive systems biology, often referred to as "postgenomics."[1]

With this aim in mind, let us first set out what we mean by postgenomics. A genome is taken to be the

1. A note on citation: Primary sources are listed in the bibliography only when quoted verbatim or paraphrased in the text. In the second part of the book in particular, the myriad of semipopular works on genomics and gene technology as well as autobiographies and biographies are not generally cited. The emphasis is on historical case studies and the discussion of particular topics, where they exist. Translations, if not otherwise stated, are our own.

totality of the hereditary material that is stored in the nuclei, as well as some other organelles like mitochondria, of living cells, usually in the form of deoxyribonucleic acid (DNA). Accordingly, genomics refers to the research field that elucidates the molecular composition and structure of whole genomes, in particular the sequence of the nucleotide base-pairs that make up the chains of DNA. The focus of genomics thus includes genes, but is not restricted to them. Technologies developed in the 1980s made it possible to characterize entire genomes at the molecular level for the first time, and since then the capacity for nucleic acid sequencing and processing the resulting sequence data has continued to grow exponentially.[2] In the first instance, the expression postgenomics simply refers to the period that began when whole genome sequencing had become feasible and the contextualization of sequence data moved center stage.

So far, so good. The completion of large-scale genomics projects like the Human Genome Project at the beginning of the new millennium coincided with the fiftieth anniversary of the elucidation of the double-helical structure of DNA (in 1953), which in turn followed roughly half a century after the identification of the gene as the fundamental unit of inheritance. Genomics, and the ensuing era of postgenomics, may therefore seem to be a logical consequence and mere extension of these epochal discoveries. But instead of experiencing closure, researchers at the dawn of the postgenomic era faced an altogether new set of questions, concerning not only the composition and structure of the genome, but its expression and integration into cell metabolism and other nongenetic processes. What was the exact relationship between genes and their products? What kind of factors spurred genes into action, and how was gene activation achieved at exactly the right time and place in an organism? And were the con-

2. At the time of putting last touches to the manuscript of this book, complete genomes of 4,050 eukaryotes, 90,849 prokaryotes, and 7,115 viruses had been sequenced; see "Genome List of National Centre for Biotechnology Information," http://www.ncbi.nlm.nih.gov/genome/browse/ (accessed 25/02/2017). GenBank, the NIH's repository for publicly available DNA sequences, counted 199,341,377 sequences in the last release of its sequence database; see "Growth of GenBank and WGS," http://www.ncbi.nlm.nih.gov/genbank/statistics (accessed 25/02/2017).

ditions of gene activation not transmitted as well, thus opening the door to the existence of nonclassical inheritance systems and deposing the gene from its privileged position as the sole bearer of hereditary information? Genetics—the science of heredity begotten by the twentieth century—is currently being buffeted by rapid and profound changes in biological thought. Even long-ignored tropes such as the inheritance of acquired characteristics appear to be experiencing a renaissance (Meloni and Testa 2014). What underlying reasons brought about this cataclysmic rethink?

According to Evelyn Fox Keller, the answer is that the "very successes [of genomics] that have so stirred our imagination have also radically undermined their core driving concept, the concept of the gene" (Keller 2000a, 5). Indeed, the centrality of the gene as the fundamental unit of biological thinking is being questioned by parts of the scientific community. Statements like the following reflect the urgency of the situation as felt even in 2007: "'Gene' has become a vague and ill-defined concept. . . . What is a 'gene'? Surprisingly, in the world of biology and genetics there is no longer a straightforward answer" (Scherrer and Jost 2007, 1). In view of this situation, some commentators have argued that we should abandon the gene concept and speak about genetic material and its expression instead (Kitcher as early as 1982; Burian 2005) or adopt more systems-oriented ways of talking about genes (Keller 2005), while still others have proposed that we need to accept the existence of a plurality of gene concepts (Moss 2003; Falk 2009; for a review of responses see El-Hani 2007). At the same time, ideas that were thought to be nongenetic and supposedly vanquished a long time ago—for example, that racial affiliation is of biomedical significance, or that maternal lifestyle may affect the hereditary constitution of the embryo—have once more become focal points of biomedical research. Talk about postgenomics, which so obviously echoes the notion of "postmodernity," also highlights the bewildering spectrum of coexisting and seemingly contradictory and anachronistic positions that have been bred by breathtaking advances in sequencing, expression profiling, and biocomputing in the last decades (Richardson and Stevens 2015).

Given this confusing backdrop, a survey from the vantage point of

the history of science is called for. What *was* the gene like to researchers at various points in the history of the discipline? we ask, and we do so not to satisfy antiquarian interests, but to provide a new understanding of this intriguing concept, an understanding that may also enable us to delineate the current horizon of the life sciences. Even the most ardent recent critics of the gene concept accept that, both as a concept and as an object of experimental and of theoretical research, the gene has been an important organizing principle in twentieth-century biology (Keller 2000a; Moss 2003; Griffiths and Stotz 2013). Nor has talk about genes vanished from scientific and vernacular discourses. On the contrary, despite apparent confusion about its meaning, talk about genes continues to be omnipresent, both within and outside the biosciences. Despite the ongoing conceptual revolution in the postgenomic biosciences, the gene is as alive and well as it was a century ago.

One might surmise that this lasting significance of the gene concept can be explained by the fact that, in the last analysis, it has always had a specific and simple meaning. But as our survey of the century of genetics and molecular biology will show, a simple and universally accepted definition of the gene *never* existed. The current situation, we will argue, is therefore nothing new. On the contrary, the gene concept always was "in flux"—as one can expect from any seminal term in the history of science (Elkana 1970; Falk 1986; Morange 2001; Weber 2005, 194–203). Right from the start, as our historical analysis will reveal, the concept of the gene took on different meanings with respect to different domains of biological reality—transmission, development, physiological function, evolution, to name just a few. And by doing so, it opened up a range of new ways to conceptualize the relationships between these domains. Speaking metaphorically, one might say that each new meaning of the gene created an additional dimension along which life could be imagined to vary and unfold.

The Danish botanist Wilhelm Johannsen recognized this open-endedness when he introduced the term "gene" into the scientific literature at the beginning of our long century of the gene. "No particular hypothesis is attached to the term gene," he wrote in 1909. In coining a new term his goal was rather to capture the idea that there is "something" in the gametes—the male and female germ cells that unite to

form the fertilized egg—that "conditions or has a determining influence on the traits of the developing organism, or has the capacity of doing so" (Johannsen 1909, 143). This definition was exceedingly vague and thus left room for all sorts of understandings of the "nature" of the gene. But that, as we claim, was precisely the point of Johannsen's "definition." As a concept, the gene referred to a distant vanishing point and connected diverse lines of research in twentieth-century biology. It did not refer to a well-defined object with a finite set of properties. Interestingly, while Johannsen denied that any hypothesis was associated with the term "gene," he also emphasized that it corresponded to a concept that already existed and "had to be named in order to become precise" (Johannsen 1909, iv). Precision and ambiguity do not exclude each other.

Attempts to give precise meanings to Johannsen's "something" proliferated throughout the twentieth century. But the operationalization of any particular definition for the purpose of experimental investigation usually only ended up revealing further puzzling phenomena that prompted ever more complex descriptions and explanations of how genes supposedly worked and influenced life (Rheinberger, Müller-Wille, and Meunier 2015). Somewhat paradoxically, one might say that the more rigidly the gene concept tried to be defined, the more questionable it became. A glance into any textbook of biology confirms that the gene can be determined in multiple frames of reference—as a unit of transmission, as a unit of mutation, as a unit of function, or as a unit of selection—and that the relations between the entities thus defined are usually not simple one-to-one but complex many-to-many relations. The much-criticized gene-centrism of the twentieth century has therefore not reduced biological reality to a purported simple core. It has revealed a forever increasing number of new entities, relations, and processes that play their role in life.

One of our overarching claims is therefore that the gene became something akin to the organizing principle of twentieth-century biology not because, once discovered, it was characterized ever more definitively, but because the object of research it referred to—the gene as an "epistemic thing" (Rheinberger 1997)—opened itself up to experimental manipulation again and again with every new turn researchers

took in providing definitions for the gene. This epistemological fertility of the gene concept points to a very special role that genes play in mediating vital processes, but not necessarily to what philosophers would call a privileged ontological status of genes as somehow more "fundamental" units to which all other phenomena of life can be "reduced." The phenomena geneticists addressed were always complex, intricate, and indeed to a large degree idiosyncratic; for otherwise they would have been of little interest to biologists. What is "fundamental" about genes must therefore likewise have something to do with the complexity and idiosyncrasy of life. The following chapter outline provides a sketch of our overall argument.

The gene, like any scientific concept, did not simply fall from heaven. Chapter 2 describes the protracted convergence in the nineteenth century of initially separate strands of investigation to a point where "heredity" became a central biological problem. We emphasize that nineteenth-century thought about heredity did not concern itself with simple phenomena, least of all with the causes of similarities between parents and offspring (e.g., in skin or eye color). The adage that "like begets like" had provided a satisfactory explanation for such similarities since ancient times. When physicians, breeders, and naturalists began to discuss heredity in the early nineteenth century, they singled out a truly exceptional and intriguing phenomenon. For they invoked the notion of heredity only in connection with a deviation—such as a disease, a malformation, or any other unusual and rare feature—that reappeared generation after generation even though its initial appearance had seemed to be an individual and capricious occurrence. Phenomena of this kind provided clues to the existence of a system of microscopic "germs" or "dispositions" that somehow spanned populations and generations and appeared to obey their own laws without always fully expressing themselves—if at all—in the manifest traits of individual organisms. Only statistical or experimental analysis could reveal the properties of such a system.

Chapters 3 and 4 focus on the rise of what is commonly known as classical genetics, covering a period that began around 1900 with the so-called rediscovery of experimental results obtained by the Augus-



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