

Preface

Influence of Epigenetic Phenomena on Gene Expression and Inheritance of Phenotypes

One of the many definitions of an epigenetic mark is a heritable feature that does not change the DNA sequence but determines when, where, and to what extent a gene will be expressed. Hence, epigenetics is a science that studies DNA packaging and regulation of its expression. Although often introduced as a new science, epigenetics dates back to the discovery of the roles of chromatin and DNA methylation in controlling gene expression in the 60s and 70s of the last century. Despite the intimate relationship between DNA and epigenetic factors, mainstream studies of genetic traits in humans and animal models have largely ignored the existence of epigenetic factors during the past decades, while the epigenetics community, although part of both the genetics and developmental biology fields, was digging deeper and deeper into the molecular mechanisms of epigenetic phenomena but seldom tackling problems of complex genetic traits in mammals. One of the reasons for the dichotomy is the very complexity of complex traits where small effects from multiple loci define the phenotype, whereas traditional molecular biology research required focusing on one selected target at a time. Another reason was the lack of methodologies capable of analyzing large amounts of epigenetic information in large cohorts of patients and controls. Nevertheless, during the last two decades, in-depth analysis of inheritance patterns combined with molecular approaches in a number of animal models, such as agouti viable yellow mice and callipyge sheep, has provided remarkable examples of how the interplay between genetic and epigenetic factors can generate complex traits.

Rapid technological improvements are now making it possible to measure epigenetic signals at many genomic locations in an unprecedented way and conduct prior-hypothesis-free epigenetic studies. Global initiatives such as the International Human Epigenome Consortium are underway to obtain high-resolution maps of histone modifications, DNA methylation, and transcription start sites and to compare epigenome signals and the resulting transcriptional regulation in a wide variety

of tissues and different cell types. However, even hypothesis-free data analyses require knowledge of epigenetic paradigms to make informed decisions when interpreting these massive data sets.

In this book, we have focused on the relationship between epigenetics and complex traits, since this field can be daunting for those wishing to do research. The biology is complex, and the ramifications of epigenetic regulation are widespread. Epigenetic states may contribute to the penetrance of genetic polymorphisms or mutations and thereby modify inheritance patterns. This may result in apparently non-Mendelian inheritance of genetic traits. Epigenetic changes in an individual may affect several different generations, depending on when these changes occur and in which cells. Genetic factors will influence epigenetic factors, and possibly their transmission. Effects may vary depending on sex, and also on the sex of an implicated parent. Concepts that applied in genetics, such as heritability, or the proportion of variance explained by genetics, can now be expanded to explicitly consider the epigenetic contributions. Furthermore, of course, different loci may demonstrate different associations with all these factors. Design of experiments and analysis of experimental data must reflect this complexity and be carefully approached.

Therefore, this book presents 14 detailed and distinct views on the interplay between complex traits and epigenetics. The chapters are grouped into three sections: (1) Fundamental aspects of the biology in epigenetics, with focus on the period in mammalian development that is pivotal for genetic transmission, i.e., gametogenesis and early embryonic development, insight into how the epigenetic marks are established, maintained, and transmitted and their influence on gene expression; (2) The known impact of epigenetic factors on several different complex traits and diseases of interest for human genetics; and (3) Approaches to experimental design and statistical analysis in this context.

Our hope is that the two communities of basic researchers and analysts will find mutual enrichment through this combination of material. An overview of available analytic methods and their underlying assumptions could inform experimental design choices. Similarly, improved understanding of the biology could lead to better choices for analysis, and an appreciation for the many factors that may need to be considered. Ultimately, this marriage of topics could lead to improved study designs, rich and complete analytic frameworks, new approaches to analysis, and guidelines for interpretation.

Of course, this book includes only a small overview of the available knowledge and approaches, yet we anticipate that this will be a helpful first reference for researchers entering the field, and will stimulate future developments. We thank Springer for making this endeavor possible.

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Epigenetics and Complex Traits

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2013, XXII, 341 p. 43 illus., 33 illus. in color., Hardcover

ISBN: 978-1-4614-8077-8