# Preface

Systems genetics is actually an old field with a new name. RA Fisher [1], S Wright [2-4], and JBS Haldane [5, 6]—the three leading figures of the *modern synthesis* who brought genetics into alignment with evolutionary biology—are the intellectual founders of what we would now call systems genetics. They used other terms—population genetics, statistical genetics, and quantitative genetics. We can add one more scientific progenitor, CH Waddington, a founder of what is now called systems biology and a key figure who helped align developmental biology with genetics [7].

The advantage of the term *systems genetics*, and the reason for its rapid rise in prominence, is that it emphasizes the concept "system" rather than the resource type (*population*), the measurement type (*quantitative*), or the method of analysis (*statistical*). Our colleague Grant Morahan coined the term in 2004 to refocus attention toward sets of related phenotypes, sets of gene variants, and sets of environmental factors and away from more restricted terms that were then in use—*genetical genomics*, *complex trait analysis*, and *QTL analysis* [8–10]. A short definition of systems genetics and its relations to other approaches may help.

Genetics can be divided roughly into three ways of looking at relations between genetic and phenotypic variation:

1. *One-to-one relations*—in other words, classical Mendelian genetics—the study of qualitative traits linked either to spontaneous mutations or to targeted modifications of genes.
2. *One-to-many relations* between single phenotypes and sets of loci or gene variants—in other words, QTL mapping, genome-wide association, and complex trait analysis.
3. *Many-to-many-to-many relations* among (a) sets of correlated and interacting phenotypes at different levels (metabolites, mRNAs, protein, organelles, cells, tissues, organ systems, and classic phenotypes and outcome measures), (b) sets of gene variants, and (c) sets of environmental factors and treatments.

The latter is the ultimate goal of systems genetics, but the reality is that we need to be working on problems at all three levels concurrently. No doubt about it: the amazing complexity and adaptability of biological systems needs to be dissected into manageable units for analytic and economic reasons. Results that make headlines and that are most highly rewarded tend to be the 1-to-1 simplifications—gene X causes aging, gene Y causes schizophrenia. But what is just as obvious now is that the yin of "dissection," "analysis," and "reduction" needs its complement—the yang of "assemble," "synthesis," and "integration."

The main motivation is not merely a scholastic intellectual balance—improved health care, agricultural productivity, and the design of robustly engineered biological systems absolutely require a deep understanding of the range of action of the whole.

The good news is that we finally have powerful tools both to dissect and to assemble biological systems with rapidly improving range, precision, and throughput. The duality of

genetics can be balanced. Generating millions of precisely measured genotypes and molecular phenotypes—our biological parts list—is now practical for thousands of cases, in principle, under many conditions. Human cohorts of millions of subjects, all sequenced and accompanied with comprehensive health records, will soon be routine. For assembly and integration of these parts, we have the computer scientists, bioinformaticists, mathematicians, statisticians, and public funders to thank for every faster and more sophisticated ways to evaluate how best to put pieces together and how to predict outcomes with some level of precision. We now can even look forward with angst to *ab initio* creation—making new biological systems from scratch. We are on the cusp of amazing capabilities.

The chapters in this volume will give you a hands-on appreciation of the range of activity and methods in systems genetics. This volume does not cover the whole range of activity; our contributors are drawn from a small but vibrant community of rodent experimental geneticists. Most of us are focused on mouse models with the goal of translational impact to better understand and cure human diseases. Most of us grew up in this new genomics era of QTL mapping, and a dominant theme of many protocols is how best to track down genetic causes of heritable variation across a wide range of systems and traits. But if you stand back and envision the whole activity represented in this volume, you will see how protocols and results can be snapped together to build more holistic models in a true systems spirit. We are now well poised to implement ever more powerful methods and models.

We thank our many colleagues, collaborators, and the 100 contributors to this volume. Both of us were frankly surprised by the highly enthusiastic responses given to our requests for protocols in this new area—no thumbscrews required. That is an excellent sign. And in keeping with the theme of systems integration, we expect that there will be strength in numbers and complementarity—that readers will, we hope, find real synergy in using collections of these protocols.

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http://www.springer.com/978-1-4939-6425-3

Systems Genetics
Methods and Protocols
Schughart, K.; Williams, R.W. (Eds.)
2017, XIV, 609 p. 164 illus., 137 illus. in color. With online files/update., Hardcover
ISBN: 978-1-4939-6425-3
A product of Humana Press