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Review

Mapping complex traits as a dynamic system

Lidan Sun [a,b], Rongling Wu [c,b,*]

[a] *National Engineering Research Center for Floriculture, College of Landscape Architecture, Beijing Forestry University, Beijing 100083, China*
[b] *Center for Statistical Genetics, Departments of Public Health Sciences and Statistics, The Pennsylvania State University, Hershey, PA 17033, USA*
[c] *Center for Computational Biology, College of Biological Sciences and Technology, Beijing Forestry University, Beijing 100083, China*

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Abstract

Despite increasing emphasis on the genetic study of quantitative traits, we are still far from being able to chart a clear picture of their genetic architecture, given an inherent complexity involved in trait formation. A competing theory for studying such complex traits has emerged by viewing their phenotypic formation as a "system" in which a high-dimensional group of interconnected components act and interact across different levels of biological organization from molecules through cells to whole organisms. This system is initiated by a machinery of DNA sequences that regulate a cascade of biochemical pathways to synthesize endophenotypes and further assemble these endophenotypes toward the end-point phenotype in virtue of various developmental changes. This review focuses on a conceptual framework for genetic mapping of complex traits by which to delineate the underlying components, interactions and mechanisms that govern the system according to biological principles and understand how these components function synergistically under the control of quantitative trait loci (QTLs) to comprise a unified whole. This framework is built by a system of differential equations that quantifies how alterations of different components lead to the global change of trait development and function, and provides a quantitative and testable platform for assessing the multiscale interplay between QTLs and development. The method will enable geneticists to shed light on the genetic complexity of any biological system and predict, alter or engineer its physiological and pathological states.

Keywords: Complex trait; Quantitative trait loci; Genetic mapping; Functional mapping; Systems mapping; Network mapping

* Corresponding author at: Center for Computational Biology, College of Biological Sciences and Technology, Beijing Forestry University, Beijing 100083, China. Tel.: +01186 (10) 6233 6283, or Center for Statistical Genetics, Departments of Public Health Sciences and Statistics, The Pennsylvania State University, Hershey, PA 17033, USA. Tel.: +1 (717) 531 2048.
E-mail addresses: rwu@bjfu.edu.cn, rwu@phs.psu.edu (R. Wu).

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1. Introduction

The past two decades have witnessed increasing applications of quantitative genetics to a wide spectrum of life sciences from plant and animal breeding to clinical medicine [16,101,118,142]. However, a considerable body of research has shown that quantitative traits are extremely difficult to study because their formation involves many unknown physiological mechanisms that guide or are guided by the underlying genetic factors that operate in a complicated way [7,100]. By regressing phenotypic values of traits directly on molecular markers from the genome, Lander and Botstein [78] have pioneered an approach for mapping and identifying specific genetic loci, known as quantitative trait loci (QTLs), that contribute to trait variation. Depending on the type of segregating populations used, this approach is called linkage mapping for controlled crosses or association mapping for natural populations [110]. With the increasing availability of inexpensive DNA sequencing and genotyping techniques, it has become a routine tool to dissect the genetic architecture of complex traits, providing unprecedented promises to construct the genotype–phenotype predictive map [62]. However, thousands of thousands of significant QTLs identified so far in a variety of species by this approach have gained little mechanistic insight because a majority of these loci have not been translated into genes and pathways [20]. The translation of functional QTLs requires knowledge of how they act and interact through a series of biochemical pathways toward the end-point phenotype.

To understand the genetic control of QTLs over the process of trait formation, a dynamic model, called functional mapping, has been developed [98,174] and recognized as an important approach for genetic mapping [69,131, 141,188]. By integrating the dynamic pathways underlying phenotypic formation using mathematical equations, this model is renovated to identify QTLs involved in rate-limiting processes and to quantify the dynamic effect pattern of these genes across a time and space scale [58,89]. More recently, functional mapping has been extended to systems mapping by viewing a phenotype as a dynamic system [46,47,91,176]. The key insight of systems mapping is that the dynamics of a complex system depends on how its elements causally influence each other by means of QTLs. By identifying QTLs that determine information flows between different elements, systems mapping can reconstruct a genotype–phenotype map from developmental pathways [12].

Many existing genetic approaches are built on a direct genotype–phenotype association. Although this is a simple strategy easy to be used, it neglects the biology inside the "black box" that links genotype and phenotype through causal networks of interacting genes and pathways. Several authors have recognized the essentiality of incorporating transcript, protein and metabolite abundance into genotype–phenotype prediction models and constructing transcriptional and regulatory networks affecting high-order phenotypes [20,101]. With these established networks, the causative and downstream effects of DNA sequences on phenotypic variation can be clearly understood by perturbing gene expression, proteins and metabolities that play a critical role in the connectivity of DNA variation through endophenotypes to the end-point phenotype.

Fig. 1 illustrates a big picture of the formation process of a complex trait from DNA to a final phenotype through a cascade of regulatory pathways. This picture presents a general system of information flow applicable for any trait or disease, but its implementation into a practical genetic study is extremely difficult, if not impossible. At the current level of biotechnology, however, it is feasible to dissolve the whole process of trait formation into multiple continuous smaller-scale systems, in each of which the comprising elements can be readily identified from prior knowledge, and further connect these systems in tandem as a functional whole. A system is defined by the elements that it constitutes, the interactions between these elements, and the natural rules of the system [113,147]. The system rules operate through individual or subsystem elements, but are effective only at the entire system level. How the function of a system is recognized and emphasized depends on the investigator or user's perspective [5].

In this review, we present a general philosophy of mapping complex traits by broadly dissecting trait formation into its three interactive underlying systems, (1) a static system of genetic architecture composed of DNA-based variants, (2) a dynamic system of morphogenesis from early to adult phenotypes, and (3) a dynamic system of regulatory networks originated from DNA and ended at the molecules as precursors for synthesizing the phenotype. Phenotypic formation of one organism may not only be affected directly by its own genes, but also indirectly by genes of its conspecific in a community. We also discuss how a dynamic system of ecological interactions determines the phenotypic variation of a complex trait. We describe the basic principle of dissecting each of these systems and the computational framework of modeling the structure, organization and function of a system through differential equations. As an approach of genetic mapping, we pinpoint several commonly used types of mapping populations that accommodate to key characteristics of different species. To the end, this review provides a dynamic strategy for using the genotype