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GENETICS:

Systems Genetics

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Abstract

Systems genetics is the next frontier in systems biology and medicine.

From studies with peas over 150 years ago, Gregor Mendel deduced the laws that govern the inheritance of traits in most organisms. The brilliance, but also the limitation, of Mendel's work was its focus on single-gene traits, such as flower color and plant height. However, phenotypic variation, including that which underlies health and disease in humans, often results from multiple interactions among numerous genetic and environmental factors. Systems genetics seeks to understand this complexity by integrating the questions and methods of systems biology with those of genetics to solve the fundamental problem of interrelating genotype and phenotype in complex traits and disease.

This global perspective is possible because of the technologies, information, and infrastructure that derive from the Human Genome Project, which sequenced the genome as a way to locate genes and other functional DNA sequence elements. These advances now allow comprehensive “-omic” measurements of RNAs, proteins, small molecules, and chemical modifications of DNA. The application of these technologies has enabled an unprecedented scale and scope of genetic and phenotypic surveys. But this does not in itself constitute a new field of study. Instead, the defining principle of systems genetics is understanding how genetic information is integrated, coordinated, and ultimately transmitted through molecular, cellular, and physiological networks to enable the higher-order functions and emergent properties of biological systems.

In contrast to the networks of molecular and physical interactions that dominate the field of systems biology, systems genetics focuses on networks of interactions between genes and traits, as well as between traits themselves. The analytical foundations for characterizing these relationships are based on graph theory and the statistics of correlation and causality (1, 2). Predictions that result from these network models can be tested with genetic mutations, chemical agents, or environmental exposures as single-factor perturbations. Machine learning methods (3) can prioritize candidate genes and network functions for further study.

Typically, gene expression levels based on global profiles have been analyzed as quantitative phenotypes, so-called eQTLs (expression quantitative trait loci) (4) to study diverse biological phenomena in yeasts, plants, flies, worms, mice, and humans. Examples range from sleep patterns in flies (5) to metabolite concentrations in plants (6). To date,

however, most of the pioneering studies in this field have focused on classically reductionist questions, such as gene discovery, rather than systems problems, such as homeostasis.

An essential but not yet fully exploited application of systems genetics is the inference of higher-order functionality in complex systems from patterns of covariation among underlying molecular and physiological phenotypes. A proof-of-concept study showed, for example, that an established inverse relationship between distinct systems, namely muscle mass and heart rate, emerged from echocardiographic measures of heart structure and function in a genetically heterogeneous population (7). Then, with single-gene mutations as perturbations, conserved and compromised network features were identified as clues to the mechanistic and systems basis for cardiac homeostasis and dysfunction. This paradigm represents a powerful strategy to solve systems problems such as the coordination of physiological functions within and among organs that are difficult to address with conventional reductionist approaches.

An important goal of systems genetics is identifying targets for modulating phenotypic outcomes to treat and prevent disease. This is difficult to achieve, however, because the sensitivity of particular trait relationships to perturbation is usually not evident. Modifier genes—variants in one gene that modulate the phenotypic manifestations of another gene—could be an efficient means of identifying such network targets. These variant genes often restore normal biological functionality despite the presence of the original disease-causing gene. Modifier effects are ubiquitous in both simple and complex traits in many organisms (8, 9). Examples in the mouse include modifiers that modulate the extent of Purkinje cell loss and dysfunction in models of neurodegenerative diseases (10), and others that control the severity of type 2 diabetes in obese mice (11). An especially exciting application of modifier genetics is the use of complete genome sequencing of families (12) that show variation in the clinical presentation of disease. With the increasing power of new technologies to provide complete genome sequences at dramatically reduced costs, systematic surveys to identify modifier genes should now be possible in humans and model organisms.

Although the goal of understanding how genetic and phenotypic variants interact to create the functional diversity of organismal biology has not changed since Mendel, the experimental and computational methods of systems genetics will finally enable studies of previously intractable problems. For example, it may be possible to determine whether genetic networks governing different biological processes (development versus physiology, for example) have distinct network features, structures, and parameters. In addition, variation in robustness, criticality, and other systems properties can be studied among individuals or populations, or in healthy versus disease states. Finally, computational models of underlying network architectures and properties can be developed to predict phenotypic outcome in response to different genetic backgrounds, environmental factors, or targeted perturbations aimed at reversing disease outcome. Systems genetics is now poised to address these and other fundamental questions in biology and medicine.

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References and Notes

1. Newman, MEJ. *Networks, An Introduction*. Oxford: Oxford Univ. Press; 2010.
2. Shipley, B. *Cause and Correlation: A User's Guide to Path Analysis, Structural Equations and Causal Inference*. Cambridge: Cambridge Univ. Press; 2002.
3. Lee SI, et al. *PLoS Genet.* 2009; 5:e1000358. [PubMed: 19180192]
4. Brem RB, Yvert G, Clinton R, Kruglyak L. *Science.* 2002; 296:752. [PubMed: 11923494]
5. Harbison ST, et al. *Nat. Genet.* 2009; 41:371. [PubMed: 19234472]
6. Keurentjes JJB, et al. *Nat. Genet.* 2006; 38:842. [PubMed: 16751770]
7. Nadeau JH, et al. *Genome Res.* 2003; 13:2082. [PubMed: 12952877]
8. Nadeau JH. *Nat. Rev. Genet.* 2001; 2:165. [PubMed: 11256068]
9. Dowell RD, et al. *Science.* 2010; 328:469. [PubMed: 20413493]
10. Lim J, et al. *Cell.* 2006; 125:801. [PubMed: 16713569]
11. Clee SM, et al. *Nat. Genet.* 2006; 38:688. [PubMed: 16682971]
12. Roach JC, et al. *Science.* 2010; 328:636. [PubMed: 20220176]

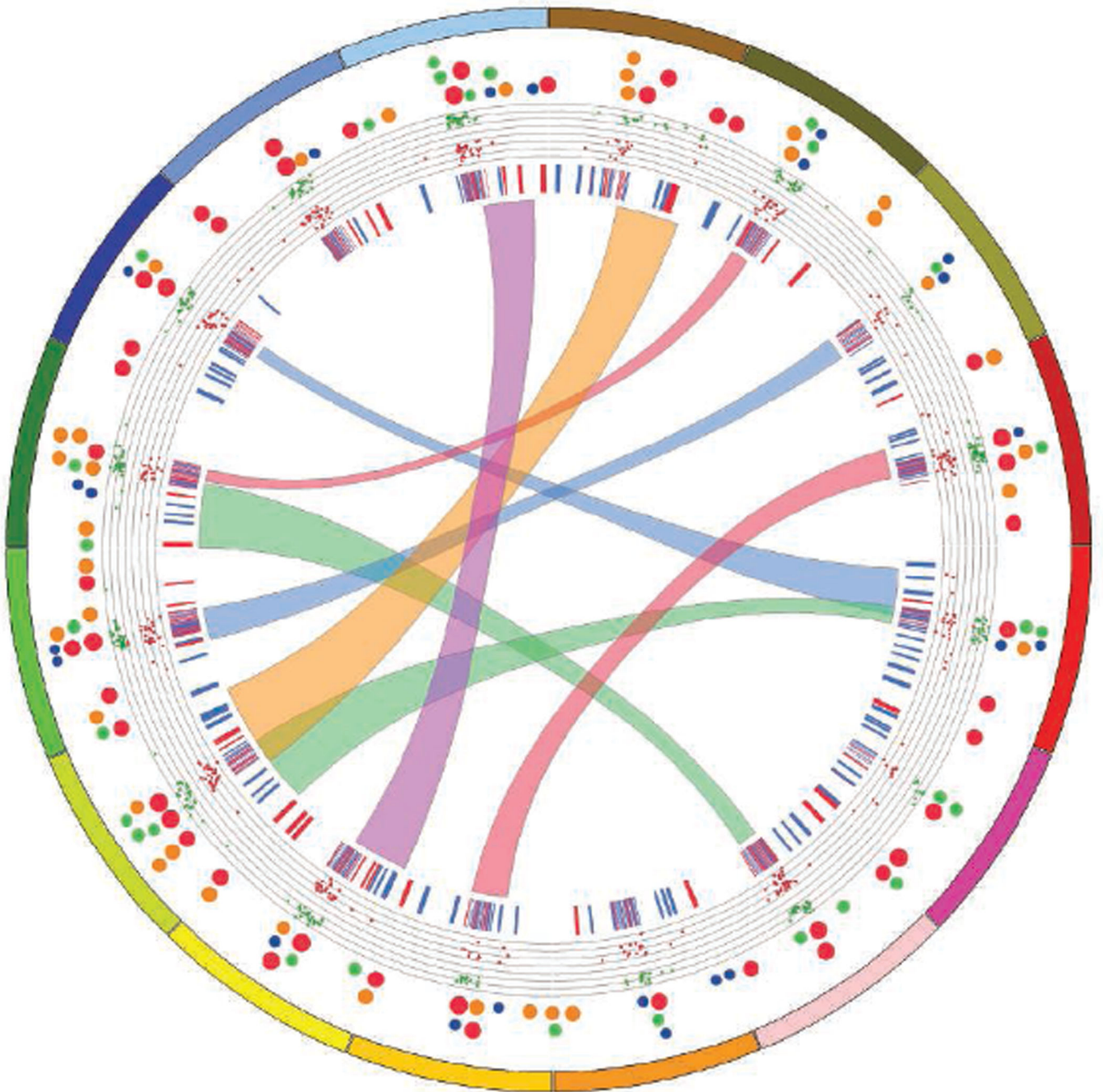


Figure 1. Multidimensional network

The image depicts the type of result one might get from a systems genetics approach (data on networks of interactions among genes and traits, for example), represented with modern visualization tools.