Journal of Biometrics & Biostatistics
ISSN: 2155-6180

Wang et al., J Biom Biostat 2012, 3:8
DOI: 10.4172/2155-6180.1000e119

Editorial Open Access

Genetic Dissection of Complex Traits: From Functional Mapping to Systems Mapping

Yaqun Wang, Ningtao Wang, Zhong Wang, Han Hao and Rongling Wu*

Center for Statistical Genetics, The Pennsylvania State University, Hershey, PA 17033, USA

Many statistical tools have been developed to map and study the genetic architecture of complex phenotypes important to agriculture, biology, and biomedicine [1-9]. Thanks to recent advances in sequencing and genotyping technologies, DNA-based marker data crucial for genetic mapping can be generated almost with no limit. A new challenge that faces methodological development is how to dissect a phenotypic trait into its biological components, study the genetic control mechanisms of these components and their mutual coordination and, ultimately, reorganize key components into a new phenotype beneficial to humans. In this editorial, we review a recent advance of statistical development that can potentially address this challenge.

From Static Mapping to Dynamic Mapping

One of the most important steps toward genetic mapping is to study dynamic changes of genetic control over phenotypic traits across a time-space continuum. This can be done by using and developing dynamic models to compare the differences of genetic control at different stages of complex traits [10-12]. Unlike the traditional static models that analyze phenotypic traits at individual time points, the central motivation of dynamic models lies in the study of the temporal pattern of genetic variation for a quantitative trait in a time course [13] and the identification of specific genes (i.e., quantitative trait loci or QTLs) that determine such a time-dependent change of the trait [14-18]. These models, called functional mapping [15], have been instrumental for detecting and mapping dynamic QTLs for individuals traits, such as stem growth and root growth in forest trees [19], plant height in rice [20], tiller number increase in rice [21], biomass growth in soybeans [22], body mass growth in mice [23,24], body height growth in humans [25] and drug response [26].

Understanding phenotypes as a dynamical system

The formation of any phenotypic trait undergoes complex interactions and coordination of its different components expressed at various organizational levels from cell to tissue to organ to organism. A full understanding of these interactive relationships among components may help shed light on the components of the biological systems and predict physiological and pathological states of the systems. This has been feasible by developing a system of differential equations that describe the dynamic behavior and coordination of the biological system based on natural laws. Below is shown a typical example for system dissection and modeling:

Consider whole-plant biomass that comprises of leaves, stem, and roots (Figure 1). However, from a mechanistic perspective, plant biomass growth is not simply the addition of these individual parts, and more importantly, entails the coordination of these parts through natural laws. Chen and Reynolds [27] used coordination theory to model the dynamic allocation of carbon to different organs by a group of differential equations. A series of allometric studies by West et al. [28] explains a power relationship existing between parts and the whole from fundamental biophysical, biochemical and evolutionary principles, i.e., plants tend to maximize leaf surface area for photosynthesis and minimize the transport distance for water, nutrients, and carbon. By integrating works by Chen and Reynolds [29] and West et al. [28], we construct a tripled group of ordinary differential equations (ODEs) to specific the coordination of leaf, stem, and root biomass for a plant :

$$\begin{aligned}\frac{dM_L}{dt} &= \alpha_L M_T^{\beta_L} - \lambda_L M_L \\ \frac{dM_S}{dt} &= \alpha_S M_T^{\beta_S} \\ \frac{dM_R}{dt} &= \alpha_R M_T^{\beta_R} - \lambda_R M_R\end{aligned} \quad (1)$$

where M_L, M_S and M_R are the biomasses of the leaves (L), the stems (S), and the roots (R), respectively, with whole-plant biomass $M_T = M_L + M_S + M_R$, α and β are the constant and exponent power of an organ biomass scaling as whole-plant biomass, and λ is the rate of eliminating ageing leave and roots. The interactions between different parts of a plant can be modeled and studied by estimating and testing the ODE parameters ($\alpha_L, \beta_L, \lambda_L, \alpha_S, \beta_S, \alpha_R, \beta_R, \lambda_R$).

Systems mapping intends to integrate a dynamic system like (1) into a mapping framework [29]. Thus, beyond static mapping and functional

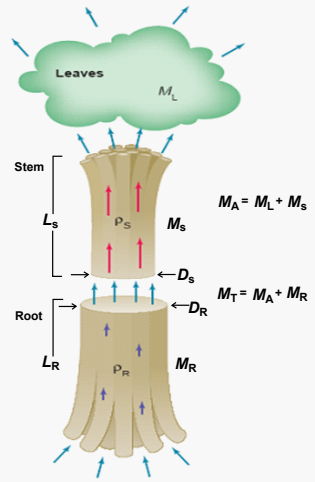

Figure 1: Leaf (L), stem (S), and root parts (R) of a plant. M: biomass, L: length, D: cross-sectional area, ρ: porosity of roots and stem. Adapted from Zens and Webb [36].

***Corresponding author:** Rongling Wu, Center for Statistical Genetics, The Pennsylvania State University, Hershey, PA 17033, USA, E-mail: rwu@phs.psu.edu

Received November 19, 2012; **Accepted** November 21, 2012; **Published** November 28, 2012

Citation: Wang Y, Wang N, Wang Z, Han H, Wu R (2012) Genetic Dissection of Complex Traits: From Functional Mapping to Systems Mapping. J Biom Biostat 3:e119. doi:10.4172/2155-6180.1000e119

mapping, this model incorporates biological and developmental mechanisms for trait formation and progression, thus equipped with power to detect the mechanistic basis of genetic actions and interactions and facilitate the test of the interplay between genes and development. Systems mapping empowers geneticists to address fundamental questions in biology and biomedicine by studying the following specific mechanistic relationships with significant impacts:

(1) Size-shape relationship: Size does matter, but shape may matter even more in nature. Shape is one of the most conspicuous aspects of an organism's phenotype and provides an intricate link between biological structure and function in changing environments. Given the parameters ($\alpha_L, \beta_L, \lambda_L, \alpha_S, \beta_S, \alpha_R, \beta_R, \lambda_R$) for system (1), one can see how much biomass has been allocated to the leaves, stem, and roots. It is possible that some plants have a dominant main stem, with less leaves, while some plants allocate more carbon to the roots (below ground) than the leaves and stem (above-ground). Thus, by integrating the ODE (1) into a QTL mapping framework, specific effects of a QTL on a plant's size and form or shape can be estimated. Furthermore, how the QTL governs the dynamic relationship between size and shape can be quantified.

(2) Structural-functional relationship: There has been a long-standing interest in understanding the relationships between structure and function. The change of structure for a system will quickly lead to the alteration of function. For a plant in drought soil, more energy should be allocated into the root system in order to increase its survival rate and fitness. If the ODE (1) is implemented with an additional fitness variable, this will constitute a dynamical system for structural-functional relationships. Genetic mapping of QTLs for such relationships will shed light on the genetic mechanisms involved in balancing vegetative and reproductive growth [30].

(3) Cause-effect relationship: A web of directed events forms a complex cause-effect relationship. The use of an antiviral drug can increase the amount of uninfected cells by reducing the load of free virus particles in a patient, which reduces the likelihood of the patient to progress into AIDS. Such cause-effect relationships between different types of cells can be quantified by differential equations [31,32]. Integrated with QTL mapping models, one can determine how specific QTLs control the dynamic changes of different types of cells in the course of time.

(4) Sink-source relationship: In plants, the function of carbohydrate source to sink relationships determines their productivity. Carbohydrates are transported from supply areas (sources) to areas of growth or storage (sinks). Carbohydrates are produced through photosynthesis in the leaves and channeled through the phloem to the roots, which act as the main carbohydrate sinks during growth. The rate of carbohydrate transport is primarily ruled by the sink strength of plant organs. A dynamic system of sink-sources relationships is composed of potential growth rate, carbon losses through growth and maintenance respiration processes, and carbon demand related to active reserve storage. The identification of specific QTLs that affect these components and therefore sink-sources relationships can be made possible by constructing a system of ODEs and integrating it with the principle of QTL mapping.

Prospects

With the emergence and development of genome-wide association studies in humans, followed by other species [33-35], it has been possible to draw a comprehensive picture of the genetic architecture of complex traits or diseases and, ultimately, integrate genetic information into genetic improvement programs or clinical therapies for disease treatment and prevention. To achieve this goal, we need to develop powerful statistical and computational algorithms for detecting genes or quantitative trait loci that determine complex phenotypes. Mathematical models and computational algorithms will be integrated within the statistical framework for genetic mapping, allowing a number of hypothesis tests to be made at the interplay between genes and the developmental pathways involved in phenotypic formation.

Acknowledgements

This work is partially supported by the Changjiang Scholars Award, "Thousand-person Plan" Award, NIH/UL1RR0330184 and NSF/IOS-0923975.

References

1. Lander ES, Botstein D (1989) Mapping Mendelian factors underlying quantitative traits using RFLP linkage maps. Genetics 121: 185–199.
2. Zeng ZB (1994) Precision mapping of quantitative trait loci. Genetics 136: 1457–1468.
3. Kao CH, Zeng ZB, Teasdale RD (1999) Multiple interval mapping for quantitative trait loci. Genetics 152: 1203–1216.
4. Sen S, Churchill GA (2001) A statistical framework for quantitative trait mapping. Genetics 159: 371–387.
5. Broman KW, Speed TP (2002) A model selection approach for the identification of quantitative trait loci in experimental crosses (with discussion). J Roy Stat Soc B 64: 641–656.
6. Wu RL, Zeng ZB (2001) Joint linkage and linkage disequilibrium mapping in natural populations. Genetics 157: 899–909.
7. Xu S (2003) Estimating polygenic effects using markers of the entire genome. Genetics 163: 789–801.
8. Jin C, Fine JP, Yandell BS (2007) A unified semiparametric framework for QTL analyses, with application to spike phenotypes. J Am Stat Assoc 102: 56–67.
9. Zou F, Nie L, Wright FA, Sen PK (2009) A robust QTL mapping procedure. J Stat Plan Infer 139: 978–989.
10. Kirkpatrick M, Heckman H (1989) A quantitative genetic model for growth, shape, reaction norms, and other infinite-dimensional characters. J Math Biol 27: 429–450.
11. Pletcher SD, Geyer CJ (1999) The genetic analysis of age-dependent traits: Modeling the character process. Genetics 153: 825–835.
12. Meyer K (2000) Random regressions to model phenotypic variation in monthly weights of Australian beef cows. Livest Prod Sci 65: 19–38.
13. Atchley WR, Cowley DE, Xu (1997) Altering developmental trajectories in mice by restricted index selection. Genetics 146: 629–640.
14. Ma CX, Casella G, Wu RL (2002) Functional mapping of quantitative trait loci underlying the character process a theoretical framework. Genetics 161: 1751–1762.
15. Wu RL, Lin M (2006) Functional mapping – A new tool to study the genetic architecture of dynamic complex traits. Nat Rev Genet 7: 229–237.
16. Macgregor S, Knott SA, White I, Visscher PM (2005) Quantitative trait locus analysis of longitudinal quantitative trait data in complex pedigrees. Genetics 171: 1365–1376.
17. Johannes F (2007) Mapping temporally varying quantitative trait loci in time-to-failure experiments. Genetics 175: 855-865.
18. Yang R, Xu S (2007) Bayesian shrinkage analysis of quantitative trait loci for dynamic traits. Genetics 176: 1169–1185.
19. Zhang B, Tong C, Yin T, Zhang X, Zhuge Q, et al. (2009) Detection of quantitative trait loci influencing growth trajectories of adventitious roots in Populus using functional mapping. Tree Genet Genom 5: 539–552.
20. Zhao W, Zhu J, Gallo-Meagher M, Wu RL (2004) A unified statistical model for functional mapping of genotype × environment interactions for ontogenetic development. Genetics 168: 1751–1762.

21. Cui YH, Zhu J, Wu RL (2006) Functional mapping for genetic control of programmed cell death. Physiol Genom 25: 458–469.

22. Li HY, Huang ZW, Wu S, Gai JY, Zeng YR, et al. (2007) A conceptual framework to mapping quantitative trait loci governing ontogenetic allometry. PLoS ONE 2(8): e1245.

23. Wu RL, Ma CX, Hou H, Corva P, Medrano JF (2005) Functional mapping of quantitative trait loci that interact with the hg mutation to regulate growth trajectories in mice. Genetics 171: 239–249.

24. Zhao W, Ma C-X, Cheverud JM, Wu RL (2004) A unifying statistical model for QTL mapping of genotype-sex interaction for developmental trajectories. Physiol Genom 19: 218–227.

25. Li N, Das K, Wu RL (2009) Functional mapping of human growth trajectories. J Theor Biol 261: 33–42.

26. Lin M, Hou W, Li HY, Johnson JA, Wu RL (2007) Modeling interactive quantitative trait nucleotides for drug response. Bioinformatics 23: 1251–1257.

27. Chen J, Reynolds J (1997) A coordination model of carbon allocation in relation to water supply. Ann Bot 80: 45–55.

28. West GB, Brown JH, Enquist BJ (1997) A general model for the origin of allometric scaling laws in biology. Science 276: 122–126.

29. Wu RL, Cao JG, Huang ZW, Wang Z, Gai JY , et al. (2011) Systems mapping: How to improve the genetic mapping of complex traits through design principles of biological systems. BMC Sys Biol 5: 84.

30. Wu RL, Ma CX, Lou XY, Casella G (2003) Molecular dissection of allometry, ontogeny, and plasticity: A genomic view of developmental biology. BioScience 53: 1041–1047.

31. Guo YQ, Luo JT,. Wang JX, Wu RL (2011) How to compute which genes control drug resistance dynamics. Drug Discov Today 16: 339–344.

32. Luo J, Hager WW, Wu R (2010) A differential equation model for functional mapping of a virus-cell dynamic system. J Math Biol 61: 1–15.

33. Allen HL, Estrada K, Lettre G, et al (2010) Hundreds of variants clustered in genomic loci and biological pathways affect human height. Nature 467: 832–838.

34. Manolio TA (2010) Genomewide association studies and assessment of the risk of disease. N Engl J Med 363: 166–176.

35. Huang XH, Wei XH, Sang T, Zhao Q, Feng Q, et al. (2010) Genome-wide association studies of 14 agronomic traits in rice landraces. Nat Genet 42: 961–967.

36. Zens MS, Webb CO (2002) Sizing up the shape of life. Science 295: 1475–1476.