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OPINION

Functional mapping — how to map and study the genetic architecture of dynamic complex traits

Rongling Wu and Min Lin

Abstract | The development of any organism is a complex dynamic process that is controlled by a network of genes as well as by environmental factors. Traditional mapping approaches for analysing phenotypic data measured at a single time point are too simple to reveal the genetic control of developmental processes. A general statistical mapping framework, called functional mapping, has been proposed to characterize, in a single step, the quantitative trait loci (QTLs) or nucleotides (QTNs) that underlie a complex dynamic trait. Functional mapping estimates mathematical parameters that describe the developmental mechanisms of trait formation and expression for each QTL or QTN. The approach provides a useful quantitative and testable framework for assessing the interplay between gene actions or interactions and developmental changes.

Most traits of biological, biomedical and agricultural importance are complex — they are under the control of an interacting network of genes, each with a small effect, and of environmental factors[1]. For this reason, the genetic study of these so-called quantitative or complex traits has long been one of the most daunting tasks in biology. Several quantitative genetic models that combine Mendelian inheritance and traditional statistical approaches, such as analysis of (co)variance, have been developed to separate the genetic and environmental effects on quantitative traits[1]. The experimental results from these models have been instrumental in providing guidance for plant and animal breeding[2] as well as evolutionary predictions for developmental events[3,4].

The rapid development of molecular technologies has allowed the generation of an almost unlimited number of markers that specify the genome structure and organization of any organism[5]. Also, improved statistical and computational techniques[6] have made it possible to tackle highly complicated genetic and genomic problems. The integration of molecular genetics and statistics has culminated in a seminal mapping paper in which Lander and Botstein[7] proposed a tractable statistical algorithm for dissecting a quantitative trait into its individual genetic locus components, referred to as quantitative trait loci (QTLs). Since then, there has been a wealth of literature concerning the development of statistical methods for mapping complex traits[8–12] and their applications in plant, animal and human genetics[13–17].

Analytical strategies for QTL mapping have been expanded to whole-genome mapping of epistatic QTLs by making use of all markers[12]. Such mapping strategies need to be carried out in an experimental cross (backcross, F_2 or full-sib family), a structured pedigree or a natural population, in which putative QTLs and markers are co-segregating owing to their physical linkage.

Although useful, traditional statistical approaches to QTL mapping neglect the developmental features of trait formation. For example, body height and weight, milk production, tumour size, HIV load, circadian clock and drug response all change with time or other independent variables and so genetic control of the trait should be accordingly represented as a function of an independent variable. An approximate approach to detecting time-dependent genetic effects for these dynamic traits has been to associate markers with phenotypes for different times or stages of development and to compare the differences across these stages[18]. More effectively, single-trait interval mapping has been

extended to accommodate the multivariate nature of time-series traits[19]. However, this extension is limited in three aspects. First, expected values of different QTL genotypes at all time points and all elements in the covariance matrix need to be estimated, resulting in substantial computational difficulties, especially when the number of time points is three or more. Second, the results might not be biologically meaningful because the underlying biological principle for the formation of dynamic traits is not incorporated. Third, statistical power to detect significant QTLs might be affected by not modelling autocorrelation between values at different time points of a trait[20], as is the case in the multivariate approach. Owing to the last two limitations, the modified approach to single-trait interval mapping cannot be effectively used in practice.

The genetic analysis of dynamic traits poses a daunting statistical challenge, which can be overcome by a general statistical framework for genome-wide mapping of specific QTLs that determine the developmental pattern of a complex trait[21–27]. Such a framework, called functional mapping, integrates the mathematical aspects of dynamic traits into the QTL mapping theory. Here we present the conceptual model for functional mapping of complex traits and provide guidelines for the experimental design of functional mapping. We begin by discussing the biological principle of functional mapping, and then examine how it can be used to unravel the genetic control of trait development. In addition, we show how functional mapping can use high-throughput SNP data to characterize quantitative trait nucleotides (QTNs).

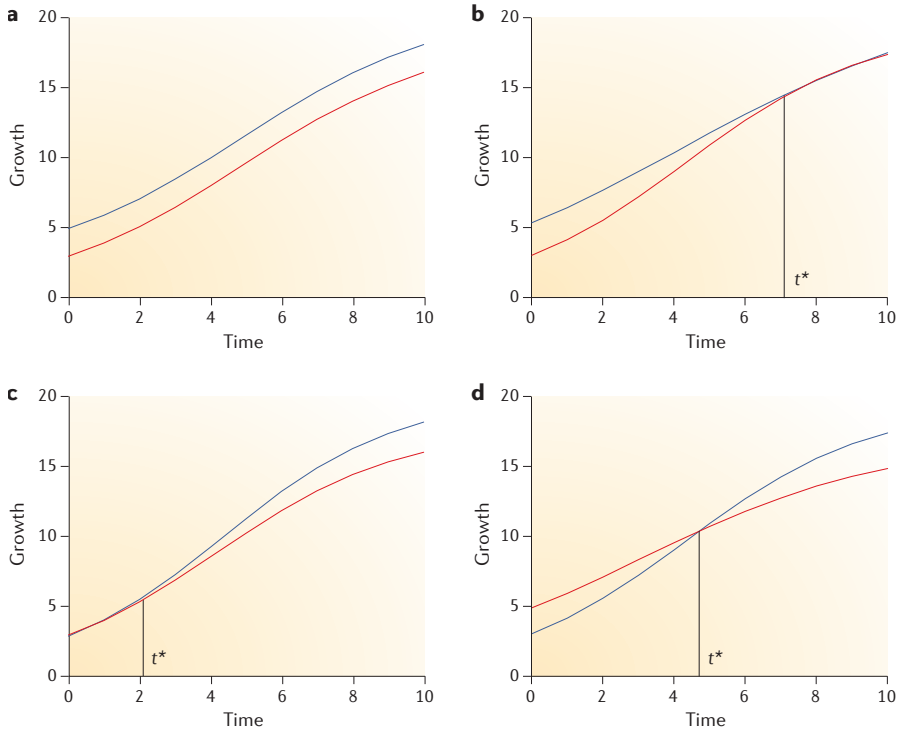


Figure 1 | **Four representative patterns for the genetic control of growth trajectories by a dynamic QTL.** Each curve represents a different QTL genotype (blue versus red). **a** | Permanent QTLs. Some QTLs are permanently expressed, which gives rise to two parallel growth curves in which one genotype is consistently better than the other throughout the entire growth process. The expression of this QTL is not affected by development, and therefore shows no interaction with age. **b** | Early QTLs. Some QTLs are expressed at early developmental stages and are switched off after a particular age. The two genotypes show different growth at early stages, but tend to converge at later stages. This QTL shows interactions with age (at time *t**) because there is a change of variance of the QTL effects during development. **c** | Late QTLs. Some QTLs remain silent during early stages and are expressed only after a particular age. The two genotypes show similar growth at early stages, but tend to diverge at later stages. Analogous to panel **b**, there is a QTL × age interaction in this case, operating with the conditional neutrality mechanism. **d** | Inverse QTLs. One genotype performs better than the other during the early stage of growth, but this changes at a later stage. This gene shows inverse effects at a particular age. Genotype × age interactions occur because there is a change of the direction of the QTL effects during development.

The dynamic patterns of genetic control

Dynamic traits vary considerably among individuals. Similarly, the patterns of genetic control that they are under vary over a given time course. FIGURE 1 illustrates four representative patterns of time-dependent genetic effects that are triggered by different QTLs. For example, some QTLs are permanently expressed, some are only turned on early in development, whereas others are turned on at specific stages in development. For each pattern shown in FIG. 1, curve parameters for developmental trajectories can be tested for individual genotypes. If different genotypes at a given QTL correspond to different trajectories, the QTL must affect the differentiation of this trait. Therefore, by estimating the curve parameters that define the trait trajectory of each QTL genotype and testing the differences in these parameters among genotypes, we can determine whether a dynamic QTL exists and how it affects the formation and expression of a trait during development.

The advantages of functional mapping

Functional mapping uses mathematical models to connect gene actions (or environmental effects) and development (BOX 1). Several mathematical functions have been established to describe the development of a phenotype and to elucidate the main characteristics of the observed patterns. For example, a series of growth equations have been derived to describe sigmoid growth curves for height, size or weight[28–31]. More recently, West *et al.*[32] explained why the growth of an organism follows a sigmoid curve on the basis of fundamental principles for the allocation of metabolic energy between maintaining existing tissue and producing new biomass.

By incorporating mathematical functions into the statistical framework for QTL mapping, functional mapping estimates genotype-specific parameters that define the developmental trajectories of a trait (BOX 2), instead of directly estimating the gene effects at all possible time points. Owing to the incorporation of biological principles (specified by mathematical models) and the need to estimate fewer parameters, functional mapping has increased statistical power to detect significant QTLs. On the other hand, estimates of the mathematical functions from functional mapping enhance the understanding of the genetic, biochemical and physiological pathways that control developmental changes. This information can be useful in preventive and curative medicine (for example, in designing gene therapy) and livestock management (for example, in selective breeding).

Within the framework of functional mapping, a series of biological questions can be asked about the genetic control of growth and development. When is a QTL switched on to affect growth and how long will the genetic effect of the QTL last? How does a QTL interact with other QTLs and with the sex or environment to determine developmental trajectories (BOX 3)? Of two possible genetic mechanisms for trait correlation, pleiotropy and linkage, which one is more important in the developmental integration of different dynamic traits? Below we discuss a series of informative tests that can be used to assess hypothetical developmental trajectories using functional mapping.

Global test. Testing whether there is a specific QTL that affects the shape of developmental trajectories is a first step towards the understanding of the genetic architecture of complex phenotypes. We can further test the global effects of different types of genetic component — additive, dominant and epistatic — on the trajectories of the trait[24].

Local test. The significance of the main (additive or dominant) effect of each QTL and the interaction (epistatic) effect between the two QTLs on development at a given time can be tested. This test can also be used to test a biologically interesting question; for example, how the dynamic QTL determines the timing at which growth reaches a predetermined size[24].

Regional test. It is likely that an important developmental event occurs over a time interval rather than simply at a time point. How QTLs exert their effects on a stage of development can be tested[24].

Interaction test. The effects of QTLs might change with age (QTL × age interaction). If the slopes of a trait trajectory (for example, growth rate) at a particular time point are different between the curves of different QTL genotypes, significant QTL × age interaction must occur between this time point and the next[24].

Test for the timing of development. Subtle changes in the timing of developmental events are a source of significant alterations in trait trajectories. Using the functional mapping model, the genetic effect of a QTL on development timing — for example, the timing of maximum growth rate — can be tested[24].

Box 1 | **Construction of functional mapping**

The statistical foundation of QTL mapping is based on the finite mixture model. According to this model, each observation (y) in a mapping population is assumed to have arisen from one (and only one) of a total of j possible components (that is, QTL genotypes); each component is modelled by a distribution density function. So, the density function of y should be expressed as the sum of component-specific densities weighted by the proportions of each component. In such a mixture model for QTL mapping, two key elements are the QTL genotype-specific densities and the component proportions — that is, the genotype frequencies of QTLs, expressed as the conditional probabilities of unknown QTL genotypes given the observed marker genotypes. The conditional probabilities of QTL genotypes are expressed in terms of the recombination fractions between the QTLs and markers for a cross pedigree or QTL–marker linkage disequilibria for a natural population. The QTL genotype-specific densities, usually assumed to be normally distributed for a quantitative trait, are specified by the expected means for different QTL genotypes and the residual variance.

For a dynamic trait that is longitudinally measured at several time points, QTL genotypic means will comprise a time-dependent vector and the residual variance will expand to form a covariance matrix of the different time points. Functional mapping models the mean time-dependent vector for different QTL genotypes using mathematical equations that describe a particular developmental process. For example, there is a logistic equation for the growth curve, a biexponential equation for HIV dynamics and a Fourier series equation for circadian rhythm. If a set of mathematical parameters that define the shape of a curve is different for different genotypes at a QTL, this implies that the proposed QTL has an effect on the process and course of development. As a result, by testing how these mathematical parameters or the variables that are derived from them are different for different genotypes at a QTL, the dynamic pattern of QTL effects that are expressed in a time course can be revealed. Because the derivation of the mathematical equation for a biological process is usually based on fundamental biological principles or mechanisms, the mathematical modelling of the mean vector used in functional mapping is biologically meaningful.

Functional mapping also models the structure of the covariance matrix using a limited number of parameters because there is a certain pattern for the autocorrelation between the phenotypic values that are measured at one time point and those that are at subsequent time points. Compared with an unstructured covariance matrix, the structured covariance matrix reduces the number of parameters to be estimated and reduces the noise level of measurements that are made repeatedly at several time points for a dynamic trait[21,84], therefore increasing the flexibility, stability and power of functional mapping.

Functional mapping has been derived for the biological processes that can be described by parametric functions, but it has now also been modified within the non-parametric context to accommodate the situation in which biologically meaningful mathematical equations do not exist[85]. Non-parametric approaches, such as random regressions[57], allow for the identification of the pattern of variation for any shape of developmental trajectories. When a high dimension of repeated measurements prevents an effective mathematical manipulation of the structured covariance matrix, a wavelet transform approach that compresses data from a high-order to low-order dimension can be incorporated into functional mapping, allowing the study of the genetic control of high-dimensional longitudinal traits (R.W. and W. Zhao, unpublished observations). Extended into large-scale gene expression or proteomic studies, such incorporation will facilitate statistically and biologically meaningful analysis of high-dimensional multivariate dynamic data.

Towards a picture of genetic architecture

The genetic architecture of complex traits can be determined in terms of gene frequencies and their additive, dominant, epistatic and pleiotropic effects in multiple environments[14,33]. Below we show how functional mapping can help our understanding of the overall picture of the genetic architecture of quantitative traits.

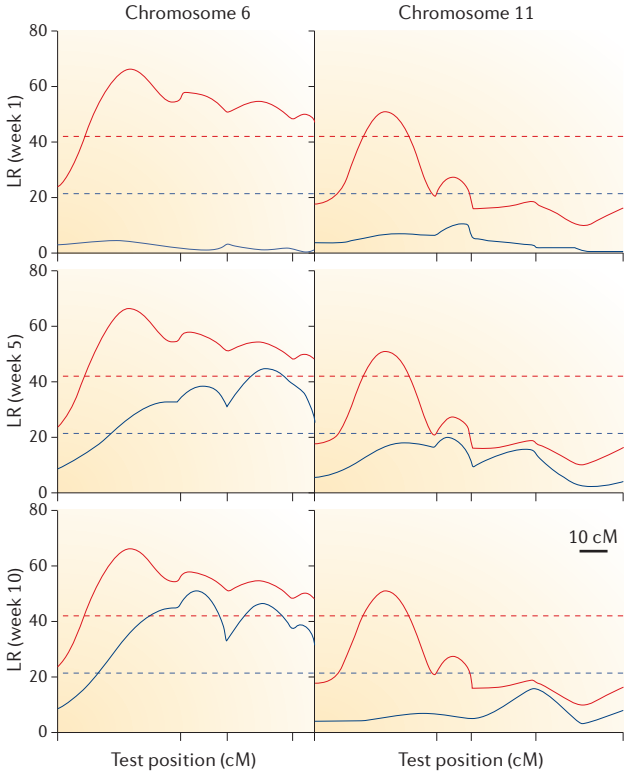
Epistatic control. Epistasis has a central role in shaping the genetic architecture of a quantitative trait[34–38]. Epistasis is also of paramount importance in the pathogenesis of most common human diseases, such as cancer and cardiovascular disease[38]. The evidence for this is the nonlinear relationship between genotype and phenotype. Epistasis has been incorporated into functional mapping of developmental trait trajectories[24]. By estimating parameters of trait trajectories for multilocus genotypes at interacting QTLs, functional mapping provides an efficient procedure for estimating and testing the effects of epistasis on the pattern and shape of developmental processes[24,39]. The model can detect the main effects of individual QTLs and the epistatic effects of the interactions between different QTLs. Various kinds of epistatic effects that result from additive × additive, additive × dominant, dominant × additive and dominant × dominant interactions[1] can be identified. For example, one can arbitrarily propose that a particular kind

Box 2 | **Functional versus interval mapping — a working example**

To demonstrate the utility of functional mapping, we analysed a real data set for an F_2 population of 535 mice that were founded by two strains, large (LG/J) and small (SM/J)[86]. The F_2 hybrids were weighed in the growth chamber at 10 weekly intervals starting at 7 days of age. The raw weights were corrected for the effect of each covariate that was due to the mother's weight, litter size at birth and parity, but not for the effect of sex, for the purpose of detecting sex-specific QTLs. From this F_2 population, 75 microsatellite markers were genotyped, with which a genetic map of the mouse genome comprising 19 chromosomes was constructed.

A genome-wide scan for sex-specific QTLs by functional mapping that incorporates a logistic growth curve and an autoregressive process detected many dynamic QTLs that govern developmental trajectories of body mass in the two sexes[47]. The figure shows the profile of log-likelihood ratio (LR) test statistics across chromosomes 6 and 11 that were found by functional mapping. The peaks of the LR profile were detected beyond the genome-wide critical threshold, which is determined from permutation tests, indicating the existence of significant dynamic QTLs at the LR peaks.

The same body-mass data were subject to traditional interval mapping[7] by choosing three representative time points at ages 1, 5 and 10 weeks, with the corresponding LR profiles calculated in a comparison with the result from functional mapping (see figure). Although traditional interval mapping detected a QTL for body weight on chromosome 6, it was not powerful enough to detect the QTL on chromosome 11. The red curve indicates the results from functional mapping, which models the mean vector by a logistic equation and the structure of covariance matrix by an autoregressive process at ages 1, 5 and 10 weeks. The blue curve indicates the results from traditional interval mapping for body weight at the same ages. The genome-wide threshold values for both methods are given as the corresponding red and blue dashed horizontal lines, which were obtained from permutation tests.



of epistatic interaction, say additive × additive, could trigger an important effect on the growth of a tumour at the time of maximum growth rate. This hypothesis can be tested with functional mapping by estimating and testing the genetic parameter that defines the additive × additive effect for the tumour growth at this time point.

Phenotypic plasticity and genotype × environment interactions. The same genotype might display different phenotypes across various environments. Genetic variation that underlies such phenotypic plasticity provides the organism with the capacity to buffer against environmental fluctuations[40,41]. Phenotypic plasticity is thought to be affected by allelic sensitivity and gene regulation[42–44]. The concept of allelic sensitivity proposes that plasticity arises from different effects of loci directly contributing to variation in plastic traits. The gene-regulation hypothesis states that specific loci influence trait changes between environments without altering trait values within a given environment. These hypotheses are not mutually exclusive, but the difference between them lies in the effect of the environment on the expression of the genes that underlie the trait: direct for allelic sensitivity, or indirect for regulatory loci[41].

Various mathematical equations have been established, either empirically or through theoretical derivations, to model the biological processes of phenotypic plasticity in response to gradients of continuous environmental factors, such as temperature[45]. By estimating the genotype-specific parameters that describe the function of the reaction norm across environmental gradients, functional mapping allows the assessment of environmental impacts on genetic variation in complex traits and testing of the two hypotheses — allelic sensitivity and gene regulation — that mediate phenotypic plasticity (see BOX 4 for the testing procedure).

Sexual dimorphism in developmental trajectories. A significant source of phenotypic variation in development is due to sex differences. The sexes of an organism represent different environments in which homologous traits can be differently expressed[46]. Variation in sexual dimorphism is equivalent to genotype × sex interaction, which occurs if a QTL affects only one sex (sex-specific effects), affects both sexes but to different degrees (sex-biased effects), or affects both sexes but in opposite directions (sex-antagonistic effects)[33]. A unifying statistical model for functional mapping of developmental trajectories that is based on sex-related differences has been proposed[47]. It allows for the detection of QTLs that contribute to sexual dimorphism in dynamic traits and for distinguishing different sex-related effects (see BOX 3 for an example).

Integrating development and plasticity. Functional mapping can be used to study dynamic patterns of genetic effects of QTLs that govern developmental trajectories and to unravel the genetic machinery of an organism's responses to different environments during the course of growth and development. In one example, plant height was repeatedly measured for a double-haploid population of rice planted in two locations with contrasting climates. Genetic analysis of growth curves using functional mapping to combine the two locations detected the existence of environment-specific QTLs for plant height[48]. Such QTLs can direct organismic development towards the best use of resources in heterogeneous environments[14].

Allometric scaling of the organism. Most variation in the metabolic rates of individuals can be due to the combined effects of two variables: body size and absolute

temperature. A series of mathematical models has been derived on the basis of biochemical kinetics and allometry to quantify the effects of size and temperature on metabolic rate[49]. Recent empirical analyses support the view that mass- and temperature-compensated metabolic rates follow a universal rule for all organisms, from microbes to forest trees to animals[49].

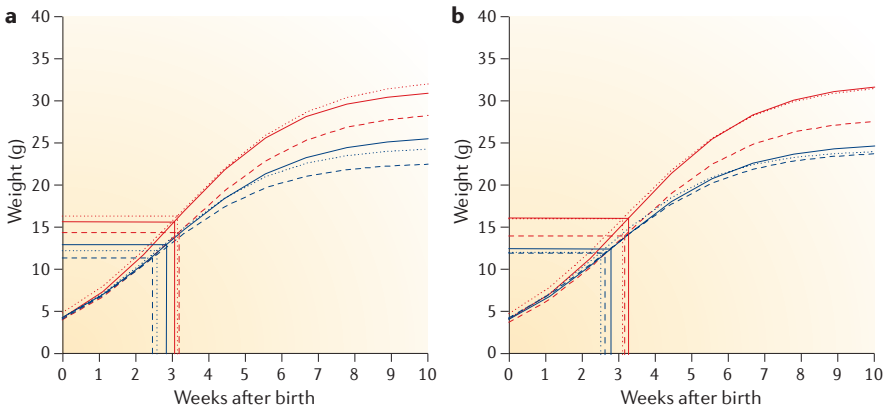
There is now a general model to explain how size and temperature affect metabolic rate. The fractal-like design of exchange surfaces and distribution networks in biological systems are thought to be responsible for whole-organism metabolic rates that are equivalent to body mass to the power of three-quarters[50–52]. Temperature increases metabolic rate exponentially through its effects on rates of biochemical reactions. However, the genetic basis for these mechanistic connections at different levels of organization is poorly understood. One promising approach is to characterize specific QTLs and genetic variants that regulate the energetics of growth, maintenance and reproduction across a biologically relevant temperature range and compare them with those genetic variants that determine the flow of energy and transformation of materials within functional ecosystems. This approach has been made possible by incorporating the allometric scaling law of the organism into the functional mapping model[23,26]. This integrated model contains the test of whether a pleiotropic QTL or linked QTL, or both, affects the correlative variation between temperature-dependent metabolic rates and body mass. It can also detect genetic variants that are responsible for the combined effects of size and temperature on metabolic rate at organizational and ecosystem levels.

Time-to-event phenotypes. Considerable recent interest has focused on the genetic control of development[53,54]. Identification of specific genetic variants that are responsible for the time-dependent CD4-positive cell count in a patient with HIV and for the time to onset of AIDS symptoms can help to design individualized drugs to control the patient's progression to AIDS. Similarly, a shared genetic basis between prostate-specific antigen — repeatedly measured for patients following treatment for prostate cancer — and the time to disease recurrence can be used to make optimal treatment schedules. Reproductive plant behaviours, such as the time to first flower and the time to form seeds, might be associated with growth rates and sizes of plants, which are the consequence of a plant's adaptation to their environment[55]. These so-called 'time to events' can be incorporated into functional mapping, with the assumption that they are controlled by QTLs that regulate developmental processes. FIGURE 2 illustrates this concept.

Deterministic and opportunistic QTLs. Specific developmental trajectories can be attributed to a complex interaction between deterministic and opportunistic factors. The deterministic factors predispose an organism towards a specific developmental trajectory (prototype), whereas the opportunistic factors modify it in response to the unique environment the organism experiences. The deterministic factors are expressed in embryogenesis, but the opportunistic factors that can be genetic or environmental occur post-embryonically. Genetic opportunistic factors are an array of new genes that are activated by the regulatory system of the organism in response to changing environments. Environmental opportunistic factors include various predictable environmental changes and unpredictable stochastic errors.

Because functional mapping can distinguish between the controlling mechanisms that are due to deterministic and opportunistic factors, it allows for the detection of deterministic QTLs (dQTLs) and opportunistic (or indeterministic) QTLs (oQTLs)[27]. dQTLs are triggered by allelic sensitivity, which is represented as the differential expression of alleles at these QTLs across development. oQTLs respond to specific environmental cues to turn on or adjust the expression of structural genes that directly influence growth. Deterministic effects occur at the level of the whole growth trajectory, basically affecting the whole growth process, whereas opportunistic effects cause deviations from the growth model by adjusting growth-rate trajectories in response to developmental signals.

Box 3 | **Dissecting genetic control of dynamic traits — a working example**



An important advantage of functional mapping is its ability to characterize the temporal patterns of the genetic control of a dynamic trait by providing a platform for testing several biologically meaningful questions, such as how each QTL affects developmental trajectories, how a QTL is expressed under different environmental conditions, and whether there is a common genetic basis for body-mass increase and the timing of development. Using the estimated parameters for growth curves of each sex-specific QTL genotype, time-dependent expression profiles of the QTLs were drawn, from which the hypotheses about the effects of genotype × sex interaction on growth curves and growth rates can be tested. The growth trajectories in the figure represent three groups of genotypes: the homozygote derived from the large (LG/J) allele (solid curve); and the heterozygote (dotted curve) and homozygote (dashed curve) derived from the small (SM/J) allele, in male (red) and female (blue) mice at the QTL identified on chromosomes 6 and 11 (BOX 2). Each inflection point indicated by the vertical lines corresponds to a specific genotype at a QTL in each sex. One QTL that was detected on chromosome 6 was significant for both males and females (panel **a**), but the modes of its action are different between the two sexes. In males, this QTL seems to be overdominant because the heterozygote outgrows the homozygote, whereas in females it operates in a partially dominant fashion as the growth trajectory of the heterozygote is between the two homozygotes. These analyses show that there are significant QTL–sex interaction effects for the QTL detected on chromosome 6 through a so-called 'sex-biased' mechanism[33]. A QTL detected on chromosome 11 exerts an effect on mass in only one sex (panel **b**). Although this QTL affects growth trajectories in a dominant fashion in males, it has no significant effect in females. The data are from Zhao *et al.*[47]

Box 4 | **Testing the hypotheses about genetic control of phenotypic plasticity**

Two general hypotheses — allelic sensitivity and gene regulation — have been proposed to explain the plastic response of complex traits to a changing environment[42]. Two studies[43,44] used a QTL mapping approach to examine these two hypotheses. The allelic-sensitivity hypothesis states that alleles have varying effects on the phenotype in different environments, which implies that the QTL affecting the sensitivity of a trait to environmental changes should map to the same region as the QTLs that explain the genetic variation in the trait within an environment. Differential expression of alleles in these QTL regions across environments would explain the covariation between trait performance and the environment.

The gene-regulation hypothesis states that special regulatory genes respond to the environment by turning on or adjusting the expression of structural genes that directly influence the trait. According to this hypothesis, the QTL regions that explain the genetic variation in phenotypic sensitivity will be distinct from those that contribute to the variation within a given environment.

The relative importance of these two hypotheses in explaining the plastic response of a complex trait can be precisely tested with functional mapping. For example, by integrating a dynamic biological thermal function into functional mapping, one can identify those 'reaction QTLs' that determine phenotypic plasticity to temperature changes. Furthermore, the incorporation of a gradient function — that is, the differentiation of the dynamic thermal function — using a procedure described in REF. 22, can lead to the detection of the 'gradient QTL' that contributes to plastic response. On the basis of these arguments, the gradient QTLs that are consistent with the reaction QTLs are thought to fit with the allelic-sensitivity hypothesis of phenotypic plasticity. The other gradient QTLs that are different from the reaction QTL are regarded as regulatory loci that have an indirect effect on plastic response.

Study designs for functional mapping

Experimental crosses. Functional mapping was originally proposed on the basis of a single experimental cross, such as the backcross, F_2 or full-sib family, initiated with two different lines[21]. The principle behind genetic mapping that uses an experimental cross is the occurrence of recombination events between genetic loci (measured by the recombination fraction) when gametes are formed and transmitted from parents to offspring. By estimating the recombination fraction between markers and QTLs, the genomic location of the QTL that affects developmental patterns of a dynamic trait can be determined.

Family-based pedigrees. For humans and some animals, neither adequate numbers of progeny can be generated from controlled crosses nor are such crosses possible. For these species, multiple related families are often used to accumulate a sufficient number of progeny for linkage analysis. However, traditional linkage strategies are not applicable for this pedigree because not all the individuals are independent from each other. When functional mapping is implemented in such a family-based pedigree, the genetic analysis of a dynamic trait can be roughly carried out in two steps. First, curve parameters that describe the dynamic change of each individual are independently estimated using a nonlinear regression approach. Second, variables of interest that are derived from these curve parameters are mapped using random-effect models that are based on identical-by-descent (IBD) relationships for each chromosomal segment between every pair of individuals[56], with the aim of estimating the genetic variances (rather than genetic effects) of each of these 'derivatives'. Alternatively, the manipulation of dynamic data for a related pedigree can be based on random regression models[57]. These models are integrated into the QTL mapping framework to estimate time-dependent genetic covariance functions for a proposed QTL and polygenes, as well as an environmental covariance function, by using various polynomials of the most parsimonious order[58].

Natural populations. For some traits, such as HIV dynamics, genetic mapping can rely only on a collection of unrelated individuals who are sampled from a natural population[59]. In this case, mapping is based on linkage disequilibrium (LD). Because a particular allele at a marker locus tends to co-segregate with one allelic variant of the gene of interest, provided the marker and gene are closely linked, LD mapping can potentially be used to map QTLs to very small regions[60]. To carry out efficient LD mapping, markers must be mapped at a density that is compatible with the distances that LD extends in the population.

Wang and Wu[61] have extended functional mapping to the LD-based identification of host QTLs that determine HIV dynamics for patients[62,63]. A similar model was derived

Glossary

Allometry
The change in proportion of various parts of an organism as a consequence of growth.

Allometric scaling law
Metabolic rates or other biological variables that scale as multiples of one-quarter of body mass.

Biexponential equation
An equation that describes two subsequent processes in which the responses change exponentially with a variable in each process.

Dynamic biological thermal function
A function that describes the change of growth rate or other variables of an organism with different temperatures.

Exercise stress test
A general screening tool to test the effect of exercise on the heart.

Finite mixture model
A type of density model that comprises several component functions, usually Gaussian functions, which are combined to provide a multimodal density.

Fourier series equation
An expansion of a periodic function in terms of an infinite sum of sines and cosines.

Linkage disequilibrium
The non-random co-segregation of alleles at different loci in a population.

Log-likelihood ratio
A test statistic that is expressed as the log ratio of the maximum value of the likelihood function under the constraint of the null hypothesis to the maximum value without that constraint.

Logistic equation
Also called an S-shaped curve. It models a process of growth in which the initial stage of growth is approximately exponential. As competition arises, the growth slows, and at maturity, growth stops.

Model selection
A process in which the best model is selected from many competing models that fit the data.

Polynomial
Functions that have the form $f(x) = a_n x^n + a_{n-1}x^{n-1} + \ldots + a_1 x + a_0$, where n is a non-negative integer.

Shrinkage estimation
An estimating procedure by which all candidate variables are taken into account in the model, but their estimated effects are forced to shrink towards zero.

Wavelet transform approach
An approach that compresses high-order dimensional data to a low-order representation without losing the original information.

for functional mapping of drug response by integrating clinically meaningful pharmacodynamic mathematical models for genetic mapping[64]. Extensive simulation studies[61,64] that are based on different clinical designs and different levels of heritability indicate that functional mapping can be effectively used to map and characterize the genetic architecture of HIV dynamics and drug response. Although LD mapping has tremendous potential to fine map QTLs for a dynamic trait, it is limited in practice because the association between a marker and QTL is also affected by evolutionary forces, such as mutation, drift, selection and admixture[1]. This disadvantage can be overcome by a mapping strategy that combines linkage and LD (see for example REFS. 11,65).

From QTL to QTN

The basic principle for QTL mapping is the co-segregation of the alleles at a QTL with those at one or a set of known polymorphic marker loci. This approach is robust and powerful for the detection of major QTLs and presents the most efficient way to use marker information when marker maps are sparse. Nevertheless, this approach has two limitations. First, because the markers and QTLs that are bracketed by them are located at different genomic positions, the significant linkage of a QTL that is detected with given markers cannot provide any information about the sequence structure and organization of QTLs. Second, the inference of the QTL's position using nearby markers will be affected by marker informativeness (expressed as the degree to which there is a correspondence between marker genotype and phenotype), marker density and type of mapping population. Consequently, only a few QTLs detected from markers have been successfully cloned[66], despite the considerable number of QTLs reported in the literature.

A more accurate and useful approach for the characterization of genetic variants that contribute to quantitative variation is to directly analyse DNA sequences that are associated with a particular disease. If a DNA sequence, or a haplotype, is known to be associated with increased disease risk, this risk can be reduced by the alteration of the string of DNA sequence using a specialized drug[67]. This risk might of course be associated with several such DNA sequences. The term QTNs describes the sequence polymorphisms that cause phenotypic variation in a quantitative trait. Liu *et al.*[68] proposed a general statistical model for the characterization of QTN variants that encode a complex phenotype in a natural population.

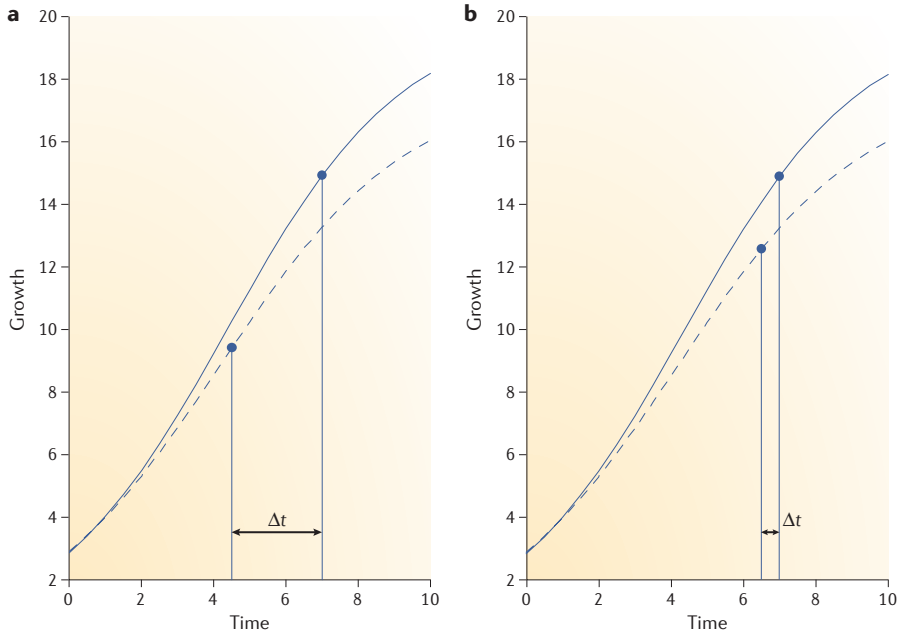


Figure 2 | **Pleiotropic QTL effects on vegetative growth and reproductive behaviour.** Suppose there are two genotypes at a QTL for which organ or tissue growth is expressed differently over time. Each genotype corresponds to 'time-to-event' phenotypes, such as survival and age at onset of a disease or flower. **a** | The QTL affects both vegetative growth and reproductive behaviour because there is a significant difference (denoted by Δ*t*) in the time to first flower between two growth QTL genotypes (represented by a solid and a dashed curve). **b** | The growth QTL does not govern reproductive behaviour because such a difference is not significant.

A strategy that is based on QTL information has been developed to identify QTNs for complex traits in controlled crosses[69].

Functional mapping, merged with the idea of QTN mapping, led to the identification of specific sequence variants that underlie developmental changes in dynamic traits. This combination of mapping approaches has enabled Lin *et al.*[70] to detect a so-called risk haplotype that is responsible for the different responses among patients to different doses of dobutamine, a drug that is designed to improve cardiovascular function for those who are unable to do an exercise stress test. The QTN-based functional mapping has further been extended to map the common genetic variants that control the trajectories of two related biological processes, such as drug efficacy and drug toxicity[71], and the effects of interactions between DNA sequences at different QTNs on the pattern and shape of a dynamic trait in a time course (M.L. and R.W., unpublished observations).

Future prospects

The traits that change with time or with any other independent variable are important in agricultural, biological and medical research. For this reason, the genetic analysis of these so-called longitudinal or dynamic traits has been a focus of several statistical and genetic studies that are aimed at predicting the dynamic change of genetic control at the genotype level[57,72–75].

More recently, a collection of statistical models for genetic mapping integrated with growth-model theories has been proposed to characterize QTLs or QTNs that govern developmental trajectories using polymorphic molecular markers[21–28,61,64] or DNA sequence data[70,71] (M.L. and R.W., unpublished observations), respectively. The basic principle of this method, called functional mapping, is to express the values of a QTL or QTN genotype at different time points in terms of a continuous function with respect to time or other independent variables. The framework for functional mapping has been built to model genetic interactions between QTLs or QTNs that are distributed across the whole genome[24] (M.L. and R.W., unpublished observations). Functional mapping, integrated with genetic information from the whole genome, through statistical approaches such as model selection or shrinkage estimation[12], allows for the complete characterization of a network of genetic interactions among all possible genes that confer the temporal pattern of variation in a complex dynamic trait.

Functional mapping as an integration of Mendelian genetics, statistics and development is superior to traditional mapping approaches that only combine Mendelian genetics with statistics. Functional mapping should be useful in agricultural and evolutionary genetics, and in medical genetic research.

In cancer clinics, the characterization of the timing at which the exponential growth phase begins and the linear growth phase ends in tumour growth enables us to determine the times from initiation to clinical symptoms, and from first symptoms to serious clinical problems[76–78]. Furthermore, it will determine how long it will take for a tumour to recur after unsuccessful treatment. It could also determine the outcome of a treatment that takes several weeks or months to complete, as is the case in many radiotherapy or chemotherapy schedules. Knowledge of the genetic control of a tumour growth rate and growth potential can be important for both prognosis and treatment[79].

Development is being integrated into evolution and ecology to create a conceptual framework for evo-devo[80–82] and eco-devo[83] in an attempt to enhance our understanding of phenotypic variation and evolution. Functional mapping links allometry, ontogeny and plasticity and provides an analytical method with which to identify the genes that regulate the integration of these phenomena[23].

Insights into the molecular and cellular targets of complex traits would offer the unprecedented opportunity to identify more precise mechanisms for growth and development. Much information has been gathered about individual cellular components at various developmental stages, but this has not yet resulted in a clear understanding of the mechanisms that control development, morphology and stress responses. Functional mapping, in conjunction with functional genomics, should give us an opportunity to study development in a comprehensive manner, and to study the dynamic network of genes that determine the physiology of an individual organism over time.

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Competing interests statement

The authors declare no competing financial interests.

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