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A GRAIENT MODEL FOR STUDYING GENOTYPE-ENVIRONMENT INTERACTIONS

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ABSTRACT

The genetic architecture of how genes interact with the environment to determine complex phenotypes remains exclusive. We know little about the genes that underlie the adaptation and microevolution of biological traits to changing environments, their number, chromosomal locations and genetic interactions as well as the environment-dependent pattern of their effects. Here we address this problem by developing a computational model for mapping specific quantitative trait loci (QTLs) that affect the gradient expression of a complex trait across a range of environments. The distinction of our model is in the incorporation of gradient changes of environmental factors into the analysis of genotype environment interactions, thereby better unraveling the attribute of quantitative traits to vary continuously in response to the environment. The model is formulated within the maximum likelihood context and implemented with a hybrid EM-simplex algorithm to estimate the model parameters. By testing the curve parameters that model environment-dependent trajectories of the trait for individual QTL genotypes, the model allows the quantitative test of a series of fundamental hypotheses about the interplay between gene action/interaction and environmental sensitivity and the prediction of genetic control over the phenotypic plasticity of any complex trait to changing environments.

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ACKNOWLEDGEMENTS

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Chapter 1

Introduction

Because a single phenotype can rarely confer high fitness in all situations, organisms are equipped with a particular internal regulatory machinery for altering their phenotypes to cope with heterogeneities in the environment [1, 2]. The capacity of such phenotypic alterations induced by the environment, called phenotypic plasticity, is thought to be under genetic control; for example, some genotypes may be more sensitive to environmental change than others [3, 4]. Understanding the genetic basis for phenotypic plasticity that leads to widespread genotype-environment interactions has been the subject of long-standing debate in biology [5, 6, 7, 8, 9, 10, 11, 12, 13, 14]. To study the degree to which genotypes vary in response to changing environments, the same genotypes are grown under multiple environmental conditions [15, 16]. Traditional analysis of (co)variance approaches are then used to test genetic, environmental, and their interaction effects and estimate the variances due to these effects and their relative contributions to the total phenotypic variance [4, 14]. Such approaches, although simple and popularly used, have a significant limitation in studying the dynamic processes of genetic control over a range of environments, thus incapable of using genetic information to predict the phenotypic changes of a trait arising from per unit change of an environmental factor.

A quantitative framework has now been proposed to describe phenotypic responses to different environments by using various forms of mathematical curves [6, 7, 18, 19, 20]. Under this framework, variability of phenotypic values produced by the same genotype when exposed to different environments, i.e., reaction norms, can be explained by mathematical parameters that define response curves. Thus, studying the genetic variation and evolution

of reaction norms becomes a statistical issue of estimating and testing these mathematical parameters. As compared to traditional approaches by which genotypic means are plotted and compared over ordered or unordered environmental states [15], this framework displays several important advantages. First, it provides a quantitative description of the change of reaction norms per unit change of an environmental factor, thus displaying a full capacity to capture every and each subtle variability in reaction norm trajectories. Second, it allows biological principles underlying phenotypic plasticity to be incorporated into the analysis of genotype-environment interactions. For example, there is a universal law that the metabolic rate of an organism increases with increasing temperature but decreases right after temperature reaches a certain value [20]. The implementation of mathematical aspects of this law will foster the biological relevance and interpretations of results. Third, mathematical modeling enables a parsimonious number of parameters to describe environment-dependent phenotypes, increasing statistical power for identifying genotype-environment interactions.

In this article, we develop a mathematical model for studying the genetic basis of phenotypic plasticity by incorporating the impact of the graded change of an environmental factor. For continuous environments, such as temperature, photoperiod, or nutrient availability, an appropriate mathematical equation of biological relevance is used to describe reaction norms as a function of the environmental factor; for example, a quadratic function quantifies the thermal performance of an insect [20, 21]. In discrete environments, such as different sexes, races, or host species for polyphagous insects, phenotypic plasticity can still be viewed as a graded response by using the environmental index as the independent variable [22]. The new model incorporates biologically meaningful mathematical equations into a statistical setting for genetic mapping based on molecular linkage maps. By testing differences in a set of mathematical parameters among genotypes at specific genes (or called quantitative trait loci, QTLs), the model can discern the significance of QTLs that trigger genetic effects on

reaction norm trajectories. By studying the dynamic behavior of genetic control exerted by individual QTLs across a continuum of an environmental factor or index, we will not only be able to study the genetic basis of variation in a complex trait, but also gain insight into the genetic basis of plastic reactions. Applied to multi-site studies of a well-known doubledhaploid (DH) rice population [16], the new model identified several environment-sensitive QTLs for plant height growth.

Chapter 2

Results

Variation in Reaction Norms.

The environmental index (EI) was calculated as the difference of the means under a particular environment and the overall mean including all the environments (including planting season and location). By plotting plant heights over the normalized EI, reaction norms for two rice varieties, indica IR64 (P1) and japonica Azucena (P2), and their progeny can be visualized as environment-dependent trajectories (Fig. 1).

The plant height for each line depends on the environmental growing conditions. Overall, all lines increases their plant height growth with increasing EI, although a particular line has decreasing growth in a certain range of EI. Parent Azucena is consistently taller over all environments than parent IR64, with the progeny displaying substantial variation in plant height trajectories. Crossovers in environment-dependent trajectories among different progeny implicates the existence of genotype-environment interactions. While most progeny have plant heights between the two parents, some transgressive segregants (i.e., those that are taller than the taller parent or shorter than the shorter parent) were identified, suggesting the complexity of inheritance of height genes.

QTL Mapping.

A total of seven QTLs were identified, named HtQ1 on chromosome 1, HtQ3 on chromosome 3, HtQ4a and HtQ4b on chromosome 4, HtQ7 on chromosome 7, and HtQ10a and HtQ10b on chromosome 10. Chromosome 4 and 10 each harbor more than one QTL, which is confirmed by composite interval mapping with better power to separate linked QTLs on a similar region of

chromosome [17]. At each QTL there are two homozygous genotypes, one composed of alleles (A) from the IR64 parent and the other composed of alleles (a) from the Azucena parent. The LOP coefficients for two different genotypes at each QTL were used to draw environment-dependent trajectories for plant height (Fig. 3). The taller Azucena parent contributes favorable alleles for plant height to its progeny at QTL HtQ1, HtQ4b and HtQ10a. However, such favorable alleles are contributed by the shorter IR64 parent at QTL HtQ3, HtQ4b, HtQ7, and HtQ10b.

Dynamic Properties of QTL-Environment Interactions.

By testing for the difference of two trajectory curves at a QTL using estimated parameters (Table 1), we can determine whether genotypes interact with environments to affect plant heights. We found that all QTLs display significant genotype-environment interactions (GEI) ($p < 1 \times 10-4$), which can be visualized by the genetic effect curves at each QTL (Fig. 4). If the effect curves are different from the zero line, this indicates the existence of GEI. According to the degree and pattern of GEI, we group the seven QTLs into four classes. The first class includes QTL HtQ1 and HtQ7 that exhibit strong GEI within a full range of observed EIs, with an increasing degree of interactions with increasing EI. The second class, composed of QTL HtQ10a, is similar to the first class but there is a smaller GEI at a lower range of EIs. The effect of this QTL has particularly a high slope of plastic response to increasing EI. The third class, i.e., QTL HtQ4b, has a moderate degree of GEI over a range of observed EIs. The last class involves three QTLs, HtQ3, HtQ4a and HtQ7, which have no pronounced GEI at a lower range of EIs but displaying increased GEI with increasing EI.

Figure Legends

Figure **1**. Trajectories of plant heights across 11 ordered environmental indices (EI) in a rice population. Each yellow line represents a DH line and two thicker lines represent two original parents, shorter IR64 and taller Azucena.

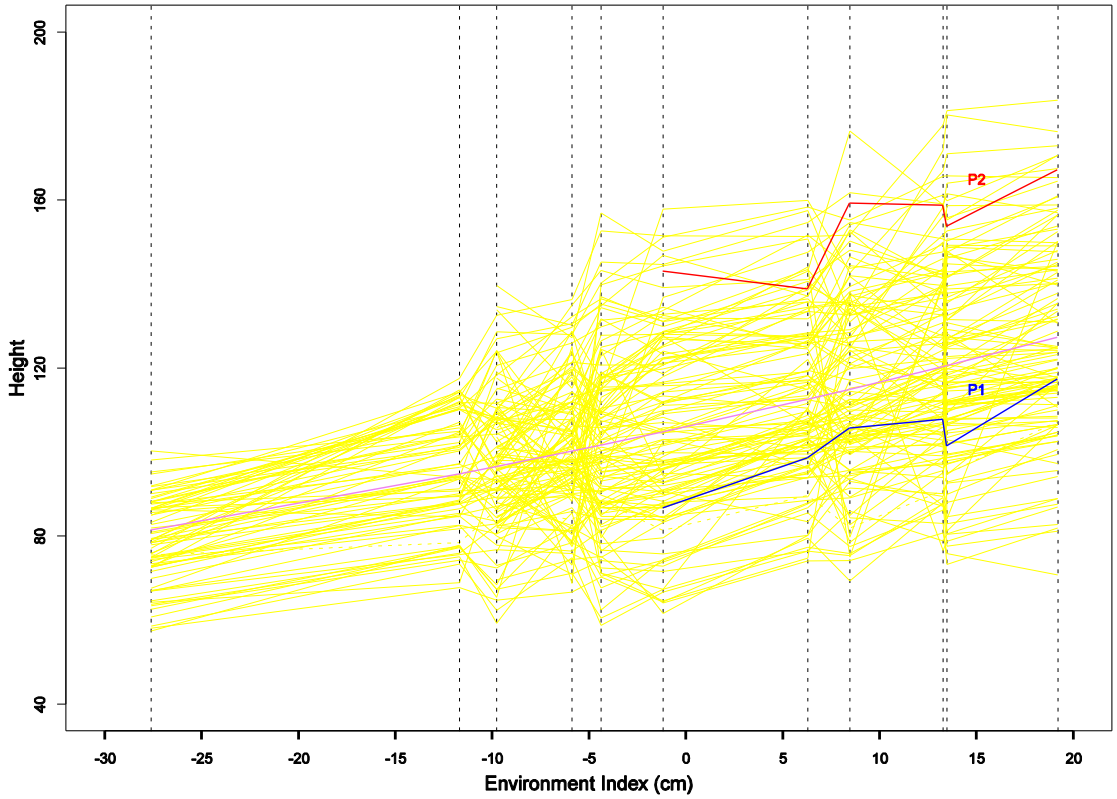

Figure **2**. The plot of log-likelihood ratios (LR) over 12 numbered rice chromosomes represented by vertical dot lines. The positions of molecular markers are shown by ticks. The genome-wide threshold at the 1% significance level, determined from 1000 permutation tests, is indicated by a red horizontal line. The positions of significant QTLs are indicated by arrowed vertical lines.

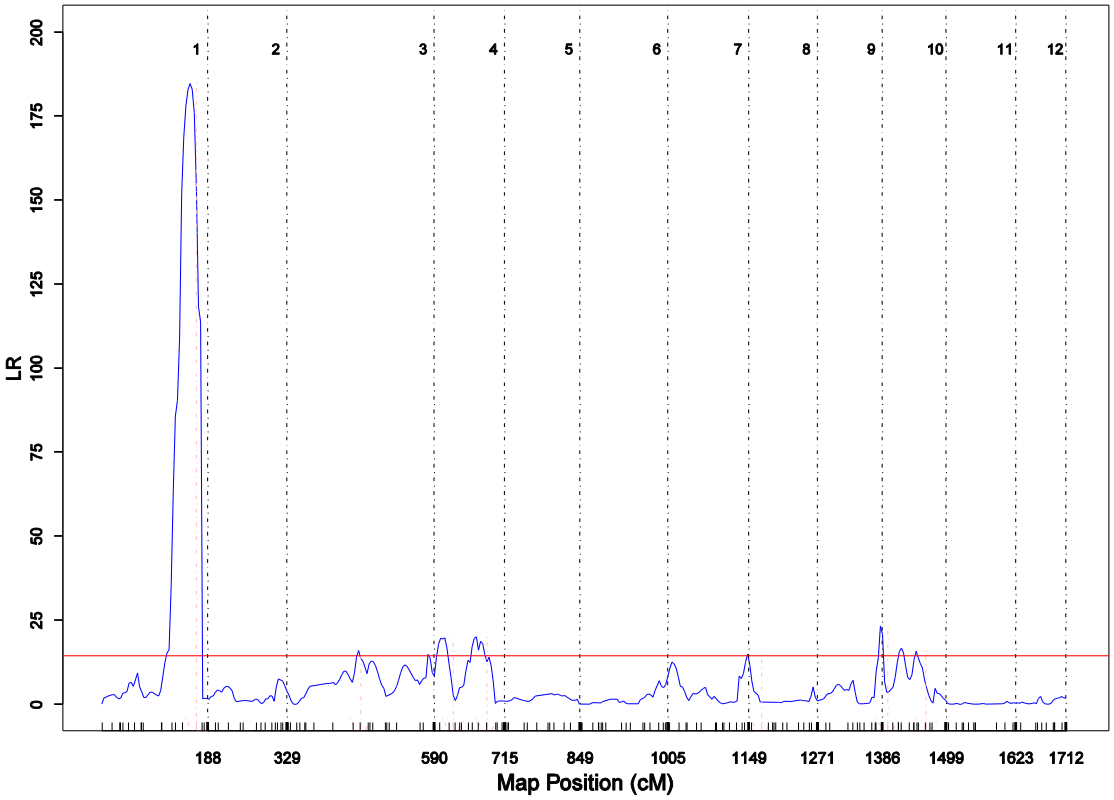

Figure **3**. Trajectory curves of environment-dependent plant heights in a DH rice population for two genotypes at each of QTLs detected on chromosome 1 (A), 3 (B), 4 (C and D), 7 (E), and 10 (F and G). Of the two genotypes, one inherits the alleles (A) from the shorter IR64 parent (blue) and the other inherits the alleles (a) from taller Azucena parent (red).

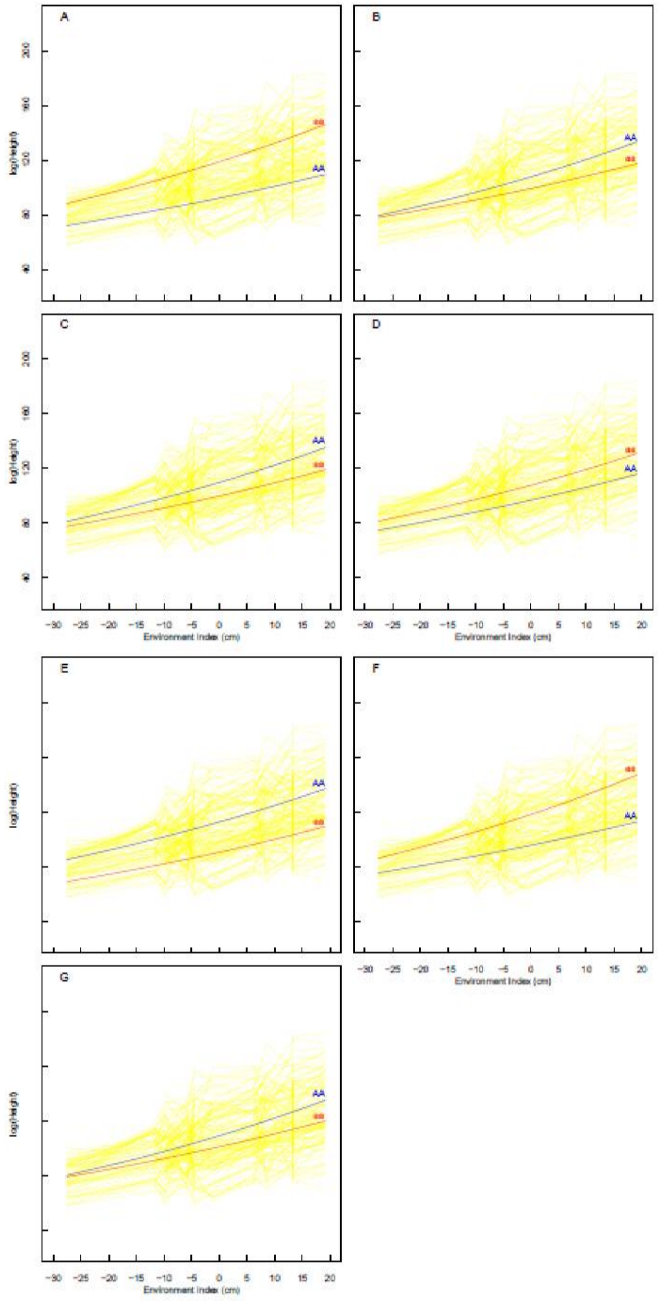

Figure **4**. Trajectories of genetic effects across a range of environments at each of the QTLs detected. The names of QTLs are shown.

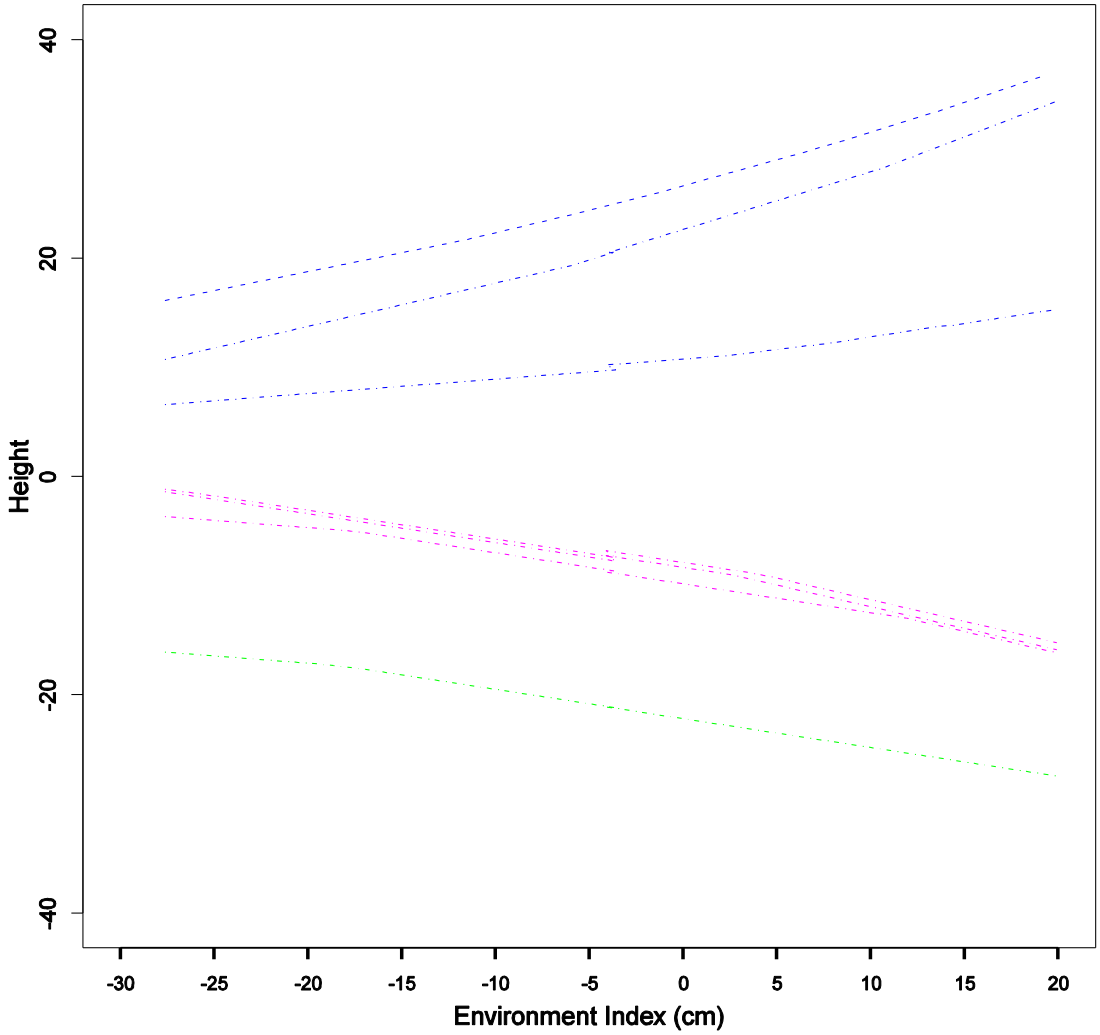

Table **1**: The QTLs and their chromosomal locations detected to affect environment dependent trajectories for plant heights. The magnitude of genetic effects at a QTL across a range of environments is defined as the difference between two genotypic curves described by two power parameters.

			AA		aa	
QTL	Chr	Marker Interval	α_1	β_1	α_2	β_2
$HtQ1$	1	RZ730-RG810	71.977	1.519	88.072	1.658
$HtQ3$	3	RZ284-pRD10A	79.262	1.682	77.85	1.507
$HtQ4a$	4	RG908-RG190	81.077	1.667	77.38	1.537
$HtQ4b$	4	RG163-RG214	74.775	1.547	81.35	1.608
$HtQ7$	7	RG20-TGMS1.2	85.262	1.609	69.150	1.585
$HtQ10a$	10	C1195-R2174	75.725	1.493	86.454	1.705
$HtQ10b$	10	G2155-RG134	79.925	1.689	78.740	1.521

Chapter 3

Discussion

The phenotype of an organism is not only controlled by its genes, but also by the environment where it grows. A growing body of evidence shows that the extent to which environment drives phenotypic changes, known as phenotypic plasticity [3, 4, 5, 7, 6, 8, 9, 10, 11, 12, 14], is also under genetic control. In a previous study measuring variation in activity level for each of the roughly 6000 genes found in yeast across a range of stressful environments, Li et al. [13] found that some genes varied enormously in their expression levels from one environment to the next, while others were relatively constant. However, without proper analysis and modeling, we would not been able to determine how many of these plastic genes are involved in the phenotypic plasticity of a biological trait.

There has been a vast amount of literature on the genetic studies of phenotypic plasticity. A majority of these studies treat the environment as being discrete and use regression models to estimate the variance due to genotype-environment interactions as a criterion to assess the genetic basis of phenotypic plasticity [15]. Founded on the established theory by several authors who view plastic response as a curve [6, 7, 18, 19, 20], we develop a conceptual model that can identify the genetic architecture of how individual genes interact with the environment to determine complex traits using quantitative trait locus (QTL) mapping based on molecular markers. Different from traditional discrete approaches in the literature, our model is able to detect QTLs that regulate the phenotypic change of a trait due to a graded change of an environmental factor. Given the fact that the evolution of quantitative traits is a continuous process [14], the new model is in a better position to be incorporated into

the context of evolutionary biology by quantifying and predicting the genetic variation of phenotypic plasticity.

Our model has several key biological meanings by embracing biological principles underlying phenotypic plasticity into the model using robust mathematical equations. First, it can identify genetic control for the origin of phenotypic plasticity; i.e., under what range of environmental conditions a QTL channels the phenotypic change of a trait through an environmental gradient. Second, the model has power to detect QTLs responsible for the rate of plastic response to environmental changes within any range of environments. Third, the model enables the integration of the genetic mechanisms for phenotypic variation in a complex trait and for the dynamic process of how the trait change its phenotype over changing environments. For example, if two phenotypes at a QTL are found to differ but parallel over a range of environments, the model suggests that this QTL controls phenotypic variation but does not exhibit genotype-environment interactions. If two different genotypes do not parallel, however, the underlying QTL does not only affect variation in trait mean, but also regulate the plastic change of the trait. Because of different dynamic features, we speculate that, compared with the former QTL, the latter QTL is more likely to direct the trait into evolution and speciation if the environment extends beyond a threshold. In addition, because of fewer parameters used to model reaction norms over no limited number of environments, our model is statistically more powerful and robust [19]. In sum, our model will help to gain a general and comprehensive view of the genetic control of phenotypic plasticity to specific environmental cues and richen our understanding of fundamental issues in evolution biology.

Chapter 4

Materials and Methods

Mapping Populations.

Two rice varieties, indica IR64 and japonica Azucena, and their 135 doubled-haploid (DH) lines were planted in seven different locations of four Asian countries (Philippines, China, India and Thailand), spanning from 13.5 degree to 31.5 degree N in latitude and from 76 degree to 121.5 degree E in longitude [16]. At one location in China, the same experiment was conducted in early and late growing seasons. Likewise, at the International Rice Research Institute of the Philippines, the experiment was performed in wet and dry seasons, in which an additional experiment was repeated with a subset of DH lines (82) in a different dry season but receiving two treatments, one under well-watered aerobic conditions and the other under water stress. Thus, a total of 11 environments were considered for genetic mapping of QTL-environment interactions. At each location, five representative plants of each line in a plot were randomly chosen to measure plant heights.

A complete linkage map for this DH population was constructed with A total of 178 markers, including 147 RFLPs, 8 isozymes, 11 RAPDs and 12 cloned genes [23]. This map, covering all 12 rice chromosomes, has a total genome size of 2,003.4 cM and an average distance of 12.4 cM between adjacent markers.

Statistical Model.

Here, we describe a general model for studying genotype-environment interactions. Consider n lines in a DH population or other types of mapping populations. These lines are planted in a particular design in *L* environments. Let $yi = (yi(1), ..., yi(L))$

denote the phenotypic data of a trait for line *i* in environment *l*. Assume that the genetic architecture of the trait involves *m* QTLs (forming 2m distinct genotypes for the DH population) which interact with each other and the environment in a complicated network to determine its final phenotype. For any one line, it should arises from one (and only one) of the 2^m possible QTL genotypes. Thus, the distribution of phenotypic data is expressed as the *J*-component mixture probability density function, i.e.,

$$y_i \sim f\left(y_i;\omega_i,\mu,\Sigma\right)=\sum_{j_1=1}^{2}\cdots\sum_{j_m=1}^{2}\omega_{j_1\ldots j_m}\left(y_i;\mu_{j_1\ldots j_m},\Sigma\right) \quad (1)$$

where $\omega_i=\left\{\omega_{j_1\ldots j_m|i}\right\}_{j_1\ldots j_m=1}^{2}$ is a vector of mixture proportions associated with different QTL genotypes $j_1\ldots j_m\left(j_1\ldots j_m=1,2\right)$ for line *i*; $\mu=\left\{\mu_{j_1\ldots j_m}\right\}_{j_1\ldots j_m=1}^{2}$ contains the mean vector of genotype $j_1\ldots j_m$ over *L* environments; and Σ contains residual variances and covariances among L environments which are common for all QTL genotypes. In genetic mapping, QTL genotypes are inferred from marker genotypes; thus, mixture proportions ω_i are actually the conditional probabilities of QTL genotypes, conditional upon the marker genotype of a particular line *i*. To derive such conditional probabilities for different types of mapping populations, see ref. [24].

The probability density function of genotype $j_1\ldots j_m$, $f_{j_1\ldots j_m}\left(y_i;\mu_{j_1\ldots j_m},\Sigma\right)$, is assumed to be multivariate normally distributed with *L*-dimensional mean vector

$$\mu_{j_1\ldots j_m}=\left(\mu_{j_1\ldots j_m}(1),\ldots,\mu_{j_1\ldots j_m}(L)\right) \quad (2)$$

and ($L \times L$) covariance matrix $\sum$. The likelihood based on a mixture model containing 2^m QTL genotypes can be written as

$$L(\Theta \mid y) = \prod_{i=1}^{n} \left[\sum_{j_1=1}^{2} \cdots \sum_{j_1=1}^{2} \omega_{j_1 \ldots j_m \mid i} f_{j_1 \ldots j_m} \left(y_i ; \mu_{j_1 \ldots j_m}, \Sigma \right) \right] \quad (3)$$

where Θ is a vector of unknown parameters including the mixture proportions, QTL genotype specific mean vectors, and (co)variances.

A traditional approach for genetic mapping with likelihood (3) is to estimate each element in the genotypic vector (2) across different environments and each element in covariance matrix $\sum$. However, this approach has the following limitations: (*i*) it does not consider biological principles under phenotypic plasticity, (*ii*) it is not parsimonious because of too many parameters being estimated, and (*iii*) because of these two above, results from this approach are difficult to be synthesized and interpreted, thereby affecting the construction of a comprehensive picture of the genetic architecture for complex traits. Below, we present a different treatment to solve likelihood (3).

Structural Modeling of Mean Vectors and (Co)variances.

It has been well known that the plastic response of a trait across a range of environments has an underlying biological basis which can be qualified by a mathematical equation. For example, the change of metabolic rates for an animal with temperature can be described by a quadratic function [7, 18, 20]. Figure 1 illustrates phenotypic trajectories of plant heights for a rice DH population of 135 lines across 11 ordered environments determined by normalized environmental indices (EI). By statistical tests, a power equation was found to adequately describe plant

height trajectories as a function of EI. Thus, we use a power equation to genotype-specific trajectories, expressed as

$$\mu_{j_1 \ldots j_m}(l) = \alpha_{j_1 \ldots j_m} x_l^{\beta_{j_1 \ldots j_m}} \quad (4)$$

where $\mu_{j_1 \ldots j_m}(l)$ is the genotypic mean of plant height for QTL genotype $j_1 \ldots j_m$ at environment l, x_l is the EI of environment l, $\alpha_{j_1 \ldots j_m}$ is the constant (intercept) of environment-dependent trajectory for genotype $j_1 \ldots j_m$, and $\beta_{j_1 \ldots j_m}$ is the power coefficient of environment-dependent trajectory for genotype $j_1 \ldots j_m$. By estimating and comparing only two parameters ($\alpha_{j_1 \ldots j_m}$, $\beta_{j_1 \ldots j_m}$) (rather than $L_{j_1 \ldots j_m}$ means) for each genotype, we will be able to determine the dynamic pattern of genetic control over environment-dependent trajectories.

For some traits whose environment-dependent expression does not obey an explicit mathematical function, nonparametric approaches, such as B-spline, can be used [25]. In many quantitative genetic analyses, a computation-efficient nonparametric approach based on Legendre orthogonal polynomials (LOP) has been used for mean and variance modeling [26, 27, 28]. Since the LOP are orthogonal to each other and integrate to 0 in the interval [-1,1], they have been applied to nonparametric regression [29], with parameter estimates possessing favorable asymptotic properties [30, 31].

The covariance matrix among phenotypic values measured at different environments may follow a structure. Many different approaches have been developed to model the covariance structure. The simplest approach is the first-order autoregressive (AR(1)) model by which variances and covariances are considered as being stationary over time. According to the AR(1) model, the variance in environment l is expressed as $\sigma^2(l) \equiv \sigma^2$ and the covariance

between environments *l* and *k* expressed as $\sigma(l,k)=\sigma\rho^{|x_l-x_k|}$ where ρ is the correlation and x_l and x_k are the EI in environment l and k, respectively. If the stationary assumptions do not hold, we will need to use a nonstationary approach, such as a structured antedependence (SAD) model [32, 33] and autoregressive moving average (ARMA) [34], for the covariance structure. In some cases, nonparametric or semiparametric approaches are a better choice [35]. Thus, instead of estimating all elements in the covariance matrix, we estimate the parameters that model the covariance structure. Zimmerman and N´u˜nez-Ant´on [32] discussed the procedures and criteria for model selection in covariance structure.

Estimation and Tests.

A hybrid EM-simplex algorithm was implemented to estimate the parameters, Θ, contained in the likelihood (3). The Θ includes QTL positions, the parameters that model genotypic mean vectors over a range of environments, and the parameters that model the covariance structure. The EM algorithm provides a platform within which the simplex algorithm is embedded to estimate Θ.

After all the parameters are estimated, we can formulate several important hypothesis tests. First, we need to test whether there is genetic control over the complex trait studied. This can be done by

$$H_0:\mu_{j_1\cdots j_m}\equiv\mu \text{ vs. } H_1:\text{ Not all equalities in the } H_0 \text{ are held } (j_1,\ldots,j_m=1,2) \quad (5)$$

from which a log-likelihood ratio (LR) test statistics is calculated. The critical threshold for claiming the significance of genetic control can be determined from permutation tests [36].

After significant genetic control is detected, we will test many biologically meaningful hypothese. The second hypothesis is about the significance of the additive, dominant, and epistatic genetic effects. Consider a pair of QTLs which form four genotypes for the DH population, with genotypic mean values in environment l, respectively, expressed as

$$\mu_{11}(l) = \mu(l) + a_1(l) + a_2(l) + i_{12}(l)$$
$$\mu_{12}(l) = \mu(l) + a_1(l) - a_2(l) - i_{12}(l)$$
$$\mu_{21}(l) = \mu(l) - a_1(l) + a_2(l) - i_{12}(l)$$
$$\mu_{22}(l) = \mu(l) - a_1(l) - a_2(l) + i_{12}(l)$$

where $\mu(l)$ is the overall mean in environment *l*,

$$a_1(l) = \frac{1}{2}\left(\mu_{11}(l) + \mu_{12}(l) - \mu_{21}(l) - \mu_{22}(l)\right)$$
$$a_2(l) = \frac{1}{2}\left(\mu_{11}(l) + \mu_{21}(l) - \mu_{12}(l) - \mu_{22}(l)\right)$$
$$i_{12}(l) = \frac{1}{2}\left(\mu_{11}(l) + \mu_{22}(l) - \mu_{12}(l) - \mu_{21}(l)\right)$$

are the additive effects of the first and second QTL in environment l, and the epistatic effect between the two QTLs in environment *l*, respectively. The null hypotheses for the additive and epistatic effects at these two QTLs are expressed as $H_0 : a_1(l) = 0, \quad H_0 : a_2(l) = 0$, and $H_0 : i_{12}(l) = 0$, respectively. The critical thresholds for each of these tests can be determined on the basis of simulation studies.

If these environment-dependent effects are significant, the third test is about the significance of genotype-enviroment interactions. The null hypotheses for these tests are expressed as

$$a_1(l) = \ldots = a_1(L) \equiv a_1 \qquad (6)$$
$$a_2(l) = \ldots = a_2(L) \equiv a_2 \qquad (7)$$
$$a_2(l) = \ldots = a_1(L) \equiv i_1 \qquad (8)$$

If the null hypothesis (6) is rejected, this means that there is a significant additive × environment interaction over a continuum of environments at the first QTL. The same is true for the second QTL. If the null hypothesis (8) is rejected, this means that an epistatic × environment interaction is significant over a range of environments. Likewise, one can be test whether a particular genetic effect interacts with a set of environments of interest. The critical thresholds for each of these genotype-environment interaction tests can be determined on the basis of simulation studies.

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