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# On the use of mathematically-derived traits in QTL mapping

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**Abstract** Mathematically-derived traits from two or more component traits, either by addition, subtraction, multiplication, or division, have been frequently used in genetics and breeding. When used in quantitative trait locus (QTL) mapping, derived traits sometimes show discrepancy with QTL identified for the component traits. We used three QTL distributions and three genetic effects models, and an actual maize mapping population, to investigate the efficiency of using derived traits in QTL mapping, and to understand the genetic and biological basis of derived-only QTL, i.e., QTL identified for a derived trait but not for any component trait. Results indicated that the detection power of the four putative QTL was consistently greater than 90% for component traits in simulated populations, each consisting of 200 recombinant inbred lines. Lower detection power and higher false discovery rate (FDR) were observed when derived traits were used. In an actual maize population, simulations were designed based on the observed QTL distributions and effects. When derived traits were used, QTL detected for both component and derived traits had comparable power, but those detected for component traits but not for derived traits had low detection power. The FDR from subtraction and division in the maize population were higher than the FDR from addition and multiplication. The use of derived traits increased the gene number, caused higher-order gene interactions than observed in component traits, and possibly complicated the linkage relationship between QTL as well. The increased complexity of the genetic architecture with derived traits may be responsible for the reduced detection power and the increased FDR. Derived-only QTL identified in practical genetic populations can be explained either as minor QTL that are not significant in QTL mapping of component traits, or as false positives.

**Keywords** Derived trait · Component trait · QTL mapping · Power analysis

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## Introduction

In the past two decades, QTL (quantitative trait locus/loci) mapping has been widely used in the genetic

study of quantitative traits. As a result, many QTL of various phenotypic traits in a wide range of species have been reported. In some QTL mapping studies, the phenotype of a trait of interest is mathematically derived from other quantitative traits, either by addition, subtraction, multiplication, or division. For convenience, traits having their own measurements and used directly in QTL mapping are called component traits or simply components throughout this study; those mathematically-derived from two or more component traits and then used in QTL mapping are called derived traits.

Derived traits are often used in genetics and breeding. In maize, the anthesis-silking interval (ASI) is an important agronomic trait related to grain yield, drought tolerance, and evolution (Bolanos and Edmeades 1996; Ribaut et al. 1996; Sari-Gorla et al. 1999; Buckler et al. 2009; Messmer et al. 2009). The phenotypic value of the ASI of a single maize plant is defined as the difference between male (MFLW) and female flowering time (FFLW). Since direct selection for drought tolerance per se is difficult in maize, ASI has been identified as an efficient indicator and is often used for selecting drought tolerant lines (Sari-Gorla et al. 1999; Ribaut and Ragot 2007). Ribaut et al. (1996) used 142 molecular markers to identify the genomic segments responsible for the expression of ASI in an $F_2$ population of 234 individuals, with the aim of developing marker-assisted selection strategies for drought tolerance (Ribaut et al. 1997; Ribaut and Ragot 2007). Mapping results showed that four QTL were common for MFLW and FFLW, one for ASI and MFLW, and four for ASI and FFLW. Two ASI-only QTL were identified, one on chromosome 2 (identified under well-watered conditions) that explained 11.4% of the phenotypic variance, and one on chromosome 6 (identified under severe stress conditions) that explained 13.0% of the phenotypic variance. Neither QTL was found for MFLW or FFLW. In a population of 142 recombinant inbred lines (RILs) and 153 markers, Sari-Gorla et al. (1999) identified five MFLW QTL, no FFLW QTL, and seven ASI QTL in well-watered environments. The ASI QTL identified on maize chromosome 9 was not identified for MFLW or FFLW. In water-stressed environments, four MFLW QTL, two FFLW QTL, and two ASI QTL were identified. The ASI QTL identified on maize chromosome 5 was not identified for MFLW or FFLW.

In rice, grain shape (GS) is an important grain quality trait defined as the ratio of grain length (GL) to grain width (GW) (Redona and Mackill 1998; Tan et al. 2000; Li et al. 2004; Rabiei et al. 2004; Aluko et al. 2004; Wan et al. 2005). In an $F_2$ population of 204 individuals and 116 molecular markers, Redona and Mackill (1998) identified seven QTL for GL, four for GW, and three for GS. The three GS QTL were controlled mostly by loci on chromosomes 3 and 7 that coincided with QTL for GL and GW. In the $F_{2:3}$ and RIL populations derived from an elite hybrid rice cultivar, Tan et al. (2000) found that major QTL for GL, GW, and GS were detected in both populations using paddy rice and brown rice, whereas minor QTL were detected only occasionally. In a rice $BC_3F_1$ population of 308 families, Li et al. (2004) identified two QTL for GL located on chromosomes 3 and 10, and one QTL for GW located on chromosome 12. Two QTL for GS were identified at similar chromosomal positions as the two GL QTL. In an $F_2$ population of 192 individuals, Rabiei et al. (2004) identified a total of 18 QTL, five for GL, seven for GW, and six for GS. Among the 18 QTL, there was one major QTL specific for GS, i.e., not detected either for GL or for GW, explaining 15% of the phenotypic variance in GS.

As indicated above, QTL mapping of derived traits sometimes shows discrepancy with QTL mapping of their components (for examples see Ribaut et al. 1996; Sari-Gorla et al. 1999; Rabiei et al. 2004; Tan et al. 2000; Wan et al. 2005). Derived-only QTL, i.e., QTL detected for derived traits but not for any component trait, have occasionally been reported. Where did the derived-only QTL come from? To what extent can we trust the derived-only QTL and use this information in breeding or other genetic studies such as QTL fine-mapping, gene cloning and marker-assisted selection? In this study, we first derived some theoretical formulas for calculating QTL effects and the genetic variance of four derived traits from two components, i.e., addition, subtraction, multiplication, and division. We then used three QTL distribution and three genetic effect models, and an actual maize mapping population, to investigate the efficiency of using derived traits in QTL mapping, and to illustrate the complexity that arises when using derived traits in QTL mapping.

## Materials and methods

### Theoretical genetic effects and genetic variance of derived traits

To demonstrate the theoretical genetic effects and the genetic variance of derived traits, we considered a four-QTL model where $Q_1$ and $Q_2$ affect component I, and $Q_3$ and $Q_4$ affect component II. Their additive effects on the two component traits are represented by $a_1$, $a_2$, $a_3$ and $a_4$, respectively. No interaction between $Q_1$ and $Q_2$ or between $Q_3$ and $Q_4$ was considered. The mean value is $m_1$ for component I, and $m_2$ for component II. Assuming that the mapping population consists of a set of RILs derived from a biparental cross, component traits in the mapping population can be classified into 16 groups based on their genotypes at the four QTL (Electronic Supplementary Material Table S1). Under the additivity assumption of QTL effects, genotypic values of the two component traits are shown in Table S1. Genotypic values of the four derived traits—addition, subtraction, multiplication, and division—were calculated from the genotypic values of the two component traits (Table S1).

On the other hand, one overall mean (denoted by $M$) and 15 genetic effects can be calculated from the 16 genotypic values given, based on Eq. 1, where the 16 genotypic values are represented by $G_1$ to $G_{16}$, respectively; $A_i$ ($i = 1, 2, 3$ and 4) denotes the additive effects of the four QTL; $A_{ij}$ denotes the additive by additive epistatic effects of two QTL ($i, j = 1, 2, 3$ and 4, and $i \neq j$); $A_{ijk}$ denotes the additive by additive by additive epistatic effects of three QTL ($i, j, k = 1, 2, 3$ and 4, and $i \neq j \neq k$); and $A_{1234}$ denotes the epistatic effects of the four QTL.The theoretical genetic effects of the two component traits and four derived traits can therefore be calculated (Table S2). As expected, for component I, $M = m_1$, $A_1 = a_1$, $A_2 = a_2$, and other genetic effects were 0. For component II, $M = m_2$, $A_3 = a_3$, $A_4 = a_4$, and other genetic effects were 0. For addition, $M = m_1 + m_2$, $A_1 = a_1$, $A_2 = a_2$, $A_3 = a_3$, $A_4 = a_4$, and other genetic effects were 0. For subtraction, $M = m_1\text{-}m_2$, $A_1 = a_1$, $A_2 = a_2$, $A_3 = \text{-}a_3$, $A_4 = \text{-}a_4$, and other genetic effects were 0 (Table S2). Interestingly, there were epistatic effects of two QTL interactions for multiplication, and epistatic effects of two and three QTL interactions for division (Table S2).

$$\begin{bmatrix} G_1 \\ G_2 \\ G_3 \\ G_4 \\ G_5 \\ G_6 \\ G_7 \\ G_8 \\ G_9 \\ G_{10} \\ G_{11} \\ G_{12} \\ G_{13} \\ G_{14} \\ G_{15} \\ G_{16} \end{bmatrix} = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & -1 & -1 & -1 \\ 1 & 1 & 1 & -1 & 1 & 1 & -1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & -1 & -1 \\ 1 & 1 & 1 & -1 & -1 & 1 & -1 & -1 & -1 & -1 & 1 & -1 & -1 & 1 & 1 & 1 \\ 1 & 1 & -1 & 1 & 1 & -1 & 1 & 1 & -1 & -1 & 1 & -1 & -1 & 1 & -1 & -1 \\ 1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & 1 \\ 1 & 1 & -1 & -1 & 1 & -1 & -1 & 1 & 1 & -1 & -1 & 1 & -1 & -1 & 1 & 1 \\ 1 & 1 & -1 & -1 & -1 & -1 & -1 & -1 & 1 & 1 & 1 & 1 & 1 & 1 & -1 & -1 \\ 1 & -1 & 1 & 1 & 1 & -1 & -1 & -1 & 1 & 1 & 1 & -1 & -1 & -1 & 1 & -1 \\ 1 & -1 & 1 & 1 & -1 & -1 & -1 & 1 & 1 & -1 & -1 & -1 & 1 & 1 & -1 & 1 \\ 1 & -1 & 1 & -1 & 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 & -1 & 1 & -1 & 1 \\ 1 & -1 & 1 & -1 & -1 & -1 & 1 & 1 & -1 & -1 & 1 & 1 & 1 & -1 & 1 & -1 \\ 1 & -1 & -1 & 1 & 1 & 1 & -1 & -1 & -1 & -1 & 1 & 1 & 1 & -1 & -1 & 1 \\ 1 & -1 & -1 & 1 & -1 & 1 & -1 & 1 & -1 & 1 & -1 & 1 & -1 & 1 & 1 & -1 \\ 1 & -1 & -1 & -1 & 1 & 1 & 1 & -1 & 1 & -1 & -1 & -1 & 1 & 1 & 1 & -1 \\ 1 & -1 & -1 & -1 & -1 & 1 & 1 & 1 & 1 & 1 & 1 & -1 & -1 & -1 & -1 & 1 \end{bmatrix} \times \begin{bmatrix} M \\ A_1 \\ A_2 \\ A_3 \\ A_4 \\ A_{12} \\ A_{13} \\ A_{14} \\ A_{23} \\ A_{24} \\ A_{34} \\ A_{123} \\ A_{124} \\ A_{134} \\ A_{234} \\ A_{1234} \end{bmatrix}. \quad (1)$$

Assuming there is no epistasis, the genetic variance of a quantitative trait in a RIL population is (Li et al. 2008):

$$V_G = \sum_{i,j=1}^{q} (1 - 2R_{ij}) a_i a_j = \sum_{i=1}^{q} a_i^2 + \sum_{j<k}^{q} 2(1 - 2R_{jk}) a_j a_k, \quad (2)$$

where $q$ is the number of QTL affecting the trait; $a_i$ and $a_j$ are the additive effects of the $i$th and $j$th QTL, respectively; $R_{ij}$ is the recombination frequency between the $i$th and $j$th QTL in the RIL population; and the relationship between $R$ and the one-meiosis recombination frequency $r$ is $R = \frac{2r}{1+2r}$, if self-pollination was repeatedly used.

## Genetic models in simulation

Assume there are ten chromosomes in a genome, each 150 cM in length and with 16 evenly distributed markers. Three distribution models of QTL location, i.e., Distributions A to C, were considered in simulation, each consisting of four QTL (denoted as $Q_1$ and $q_1$–$Q_4$ and $q_4$ or simply $Q_1$–$Q_4$; Table 1). $Q_1$ and $Q_2$ affect component I, and $Q_3$ and $Q_4$ affect component II. In Distribution A, the four QTL were located on chromosomes 1–4, and their chromosomal positions were at 18, 28, 53, and 63 cM, respectively. A linkage of 35 cM was considered in Distributions B and C on the first two chromosomes. In Distribution B, $Q_1$ and $Q_2$ were linked on chromosome 1, and $Q_3$ and $Q_4$ were linked on chromosome 2. In Distribution C, $Q_1$ and $Q_3$ were linked on chromosome 1, while $Q_2$ and $Q_4$ were linked on chromosome 2 (Table 1).

**Table 1** Three distribution models for four QTL locations in the simulation study

| QTL | Trait affected | Distribution A | | Distribution B | | Distribution C | |
|---|---|---|---|---|---|---|---|
| | | Chr. | Pos. (cM) | Chr. | Pos. (cM) | Chr. | Pos. (cM) |
| $Q_1$ | Component I | 1 | 18.0 | 1 | 18.0 | 1 | 18.0 |
| $Q_2$ | Component I | 2 | 28.0 | 1 | 53.0 | 2 | 28.0 |
| $Q_3$ | Component II | 3 | 53.0 | 2 | 28.0 | 1 | 53.0 |
| $Q_4$ | Component II | 4 | 63.0 | 2 | 63.0 | 2 | 63.0 |

*Chr* chromosome, *Pos* position

**Table 2** Three genetic effect models in the simulation study

| Genetic parameter | Effect A | Effect B | Effect C |
|---|---|---|---|
| Additive effect of $Q_1$ on component I ($a_1$) | 1.0 | 1.0 | 0.0 |
| Additive effect of $Q_2$ on component I ($a_2$) | 1.0 | 1.0 | 0.0 |
| Additive effect of $Q_3$ on component II ($a_3$) | 1.0 | 1.0 | 0.0 |
| Additive effect of $Q_4$ on component II ($a_4$) | 1.0 | 1.0 | 0.0 |
| Additive by additive effect between $Q_1$ and $Q_2$ ($aa_{12}$) | 0.0 | 1.0 | 1.0 |
| Additive by additive effect between $Q_3$ and $Q_4$ ($aa_{34}$) | 0.0 | 1.0 | 1.0 |

For each distribution model, three genetic effect models were simulated (Table 2), i.e., Effect A: the pure additive model, where component QTL only have additive effects; Effect B: the additive and epistasis model, where component QTL have both additive and epistatic effects; and Effect C: the pure epistasis model, where component QTL have epistatic effects but do not have additive effects. In Effect A, the additive effects of the four QTL were all set at 1.0. No epistatic effect was assumed between $Q_1$ and $Q_2$ or between $Q_3$ and $Q_4$. In Effect B, the additive effects of the four QTL, and the additive by additive epistatic effects between $Q_1$ and $Q_2$, and $Q_3$ and $Q_4$, were all set at 1.0. In Effect C, the additive by additive epistatic effects between $Q_1$ and $Q_2$, and $Q_3$ and $Q_4$, were both set at 1.0. None of the four QTL was assumed to have additive effects. The mean value was set at 25 for trait I, and at 20 for trait II, for the three effect models.

According to the theoretical formulas in the previous section, genetic variances for component traits I and II and derived traits addition and subtraction can be easily calculated for Effect A (Tables 2 and S2). For multiplication and division, the genetic architecture becomes very complicated, as additive by additive epistatic effects and even three-dimensional epistatic effects for division have to be considered simultaneously. Formulas for the genetic variances of derived traits multiplication and division are not given in Table S2. Genetic effects of the four QTL and the genetic variance under Effect A and Distributions A–C are given in Table S3 for component and derived traits. By definition, broad-sense

heritability ($H$) is the total genetic variance ($V_G$) divided by the total phenotypic variance ($V_P$), i.e.,

$$H = \frac{V_G}{V_P} = \frac{V_G}{V_G + V_\varepsilon}. \quad (3)$$

In simulation, $V_G$ was calculated from the predefined QTL effect for each of Distributions A–C, and the error variance ($V_\varepsilon$) was fixed at 4.67 for the two component traits. Thus for traits I and II under Effect A, the theoretical $H$ was 0.30 in Distributions A and C, and 0.39 in Distribution B due to the increased genetic variance caused by the coupling linkage (Tables 1 and S3).

## An actual maize RIL population

One biparental population in the maize NAM design (Buckler et al. 2009), consisting of 187 RILs, was used to construct a QTL distribution and effect model that is more realistic compared with previous distribution and effect models. The linkage map was based on 756 markers, which covered 1,380.8 cM of the ten maize chromosomes, with an average distance of 1.85 cM between markers. Component I is female flowering time (FFLW), and II is male flowering time (MFLW). The phenotypic distribution of FFLW and MFLW is shown in Fig. 1. The minimum, mean, and maximum phenotypic values (days) are 73.44, 81.47, and 91.11 for trait I, and 72.50, 78.40, and 86.78 for trait II, respectively. Positive correlation was observed between FFLW and MFLW (Fig. 1). Phenotypic values of the four derived traits were the addition, subtraction, multiplication, and division of each component from traits I and II, respectively.

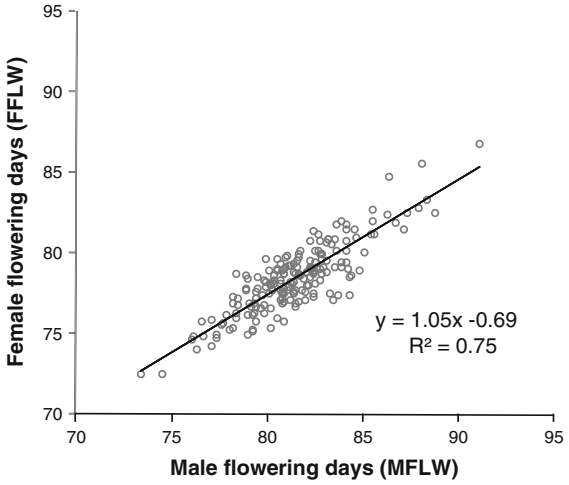


**Fig. 1** Phenotypic distribution of two component traits in a maize population consisting of 187 recombinant inbred lines

## Population simulation and QTL mapping in simulated populations

With the software QTL IciMapping (available from http://www.isbreeding.net), 1,000 populations, each consisting of 200 RILs, were generated for the above QTL distribution and effect models. Phenotypic values of component traits were defined from the corresponding genetic models, from which the derived traits were calculated. QTL mapping in each simulated population was conducted by inclusive composite interval mapping (ICIM; Li et al. 2007 and Wang 2009) implemented in the QTL IciMapping software. In ICIM, marker selection is conducted only once through stepwise regression by considering all marker information simultaneously; phenotypic values are then adjusted by all markers retained in the regression equation, except the two markers flanking the current mapping interval (Li et al. 2007; Wang 2009). In this simulation study, the probabilities of a marker entering into the model and moving out of the model were set at 0.01 and 0.02, respectively. The LOD threshold of 2.5 was used to declare the significant QTL. These parameters were also used in QTL mapping of the actual maize population.

Two methodologies were used to calculate QTL detection power through simulation, as adopted in Li et al. (2007) and Zhang et al. (2008). Firstly, each pre-defined QTL was assigned to a support interval with the true QTL in the middle; then the power was estimated for the defined support interval. In this case, QTL detected in other intervals were counted as false positives. False discovery rates (FDR) were calculated as the ratio of false QTL to all significant QTL. Each support interval was 10 cM in length in the power analysis. Average position and effect estimates were performed on simulated populations where higher-than-threshold peaks in the support intervals were observed. Secondly, the power was calculated for each interval defined by two flanking markers. Power calculated in this way allows us to investigate the distribution of all significant QTL in the genome. No false QTL were counted in this case.

## Results

### QTL detection power in putative QTL distribution and effect models

For Effect A, detection power of the four QTL in the 10 cM support interval was consistently high for component traits under the three QTL distribution models, i.e., 91.90–95.40% (Table 3). Detection power was slightly lower for $Q_2$ and $Q_4$ in Distribution B, due to the linkage between $Q_1$ and $Q_2$, and between $Q_3$ and $Q_4$ (Tables 1 and 2). FDR was around 22%, and position and effect estimates (Table 3) were close to their true values (Tables 1 and 2) regardless of the QTL distributions. Much lower detection power and higher FDR were observed for all derived traits under all distribution models (Table 3).

The reduction in power when using derived traits can be explained by the larger QTL number and by the fact that more complicated genetic effects are associated with derived traits (Tables 3 and S2). For Effect A, only additive effects of two QTL were involved in each component trait. However, four QTL affect each derived trait. Other genetic effects as well as the additives are present for derived traits such as multiplication and division (Tables 3, S2 and S3), which complicated the one-dimensional scanning process for additive QTL. Multiplication of two component traits can cause digenic QTL interactions (i.e., $A_{13}$, $A_{14}$, $A_{23}$, $A_{24}$, and $A_{34}$ in Tables S2 and S3), and division can even cause interactions among three QTL (i.e., $A_{134}$ among $Q_1$, $Q_3$, and $Q_4$, and $A_{234}$ among $Q_2$, $Q_3$, and $Q_4$ in Tables S2 and S3). The increased QTL number and more complicated genetic effects actually reduce the additive genetic variance and, consequently, QTL detection power. For example, in Distribution A, $Q_1$ explains 50% of genotypic variance for component trait I. When addition or subtraction is used, $Q_1$ explains 25% of genotypic variance (calculated from Table S3). When multiplication and division are used, $Q_1$ explains only 19.46% of genotypic variance (calculated from Table S3). Thus reduced power is expected when a derived trait is used in QTL mapping.

Addition and subtraction have similar detection power in Distribution A, and multiplication and division have similar detection power in Distributions A and B (Table 3). However, in Distribution C, addition has much higher detection power than subtraction, and multiplication has much higher detection power than division (Table 3), since the repulsive linkage between $Q_1$ and $Q_3$, and between $Q_2$ and $Q_4$, is present in subtraction and division (Tables 1 and 3). Repulsive linkage reduces genetic variance (Table S3), and therefore reduces heritability as well, resulting in a reduction in detection power. On the contrary, coupling linkage increases genetic variance and therefore increases heritability, which gives rise to increased detection power. Though detection power was reduced for derived traits, almost unbiased position estimation was nonetheless achieved (Table 3). Genetic effects were all over-estimated (Table 3) compared with their theoretical effects (Table S3). For instance, for multiplication, the theoretical additive effects were 20 for $Q_1$ and $Q_2$, and 25 for $Q_3$ and $Q_4$. The estimated effects of $Q_1$ and $Q_2$ were approximately 23 in Distribution A, 25 in Distribution B, and 25 in Distribution C; the estimated effects of $Q_3$ and $Q_4$ were around 27 under all models. Over-estimation of QTL effects in simulation studies has been explained in Li et al. (2007) and Zhang et al. (2008).

In the marker-interval power analysis, four clear peaks were observed around the four predefined QTL of two component and four derived traits for the three distribution models (Fig. 2). The four clear peaks were not affected when we included epistasis between $Q_1$ and $Q_2$, and between $Q_3$ and $Q_4$, i.e., for Effect B (Fig. S1). In both cases (Figs. 2 and S1), the power was close to 0 in other chromosomal regions. If there were only two epistatic effects between $Q_1$ and $Q_2$, and between $Q_3$ and $Q_4$, and none of $Q_1$–$Q_4$ had additive effects, i.e., Effect C, significant peaks were randomly distributed and close to 0 across the whole genome for two component and four derived traits (Fig. S3). Marker-interval power analysis did not identify certain chromosomal regions with significant high frequency of additive QTL when using the four derived traits in QTL mapping. Results from Effect C indicate that epistasis between QTL controlling component traits is less likely to cause derived-only QTL when derived traits are used in QTL mapping.

### QTL distribution and effect model in the maize RIL population

For the two component traits (I for MFLW, II for FFLW) in the maize RIL population, 11 additive

**Table 3** Simulation results of the pure additive genetic model (i.e., Effect A) for the three distribution models defined in Table 1

| Distribution | Parameter | QTL | Trait I | Trait II | Addition | Subtraction | Multiplication | Division |
|---|---|---|---|---|---|---|---|---|
| A | Power (%) | $Q_1$ | 95.10 | | 69.60 | 69.30 | 55.20 | 50.50 |
| | | $Q_2$ | 94.80 | | 69.80 | 70.40 | 54.10 | 50.90 |
| | | $Q_3$ | | 92.50 | 67.20 | 65.30 | 76.90 | 75.20 |
| | | $Q_4$ | | 94.50 | 68.40 | 65.40 | 77.80 | 75.20 |
| | FDR (%) | | 21.63 | 22.98 | 27.42 | 28.05 | 28.07 | 29.68 |
| | Estimated position (cM) | $Q_1$ | 18.54 (2.36) | | 18.55 (2.48) | 18.62 (2.57) | 18.36 (2.56) | 18.45 (2.56) |
| | | $Q_2$ | 28.46 (2.28) | | 28.49 (2.52) | 28.38 (2.56) | 28.44 (2.53) | 28.52 (2.56) |
| | | $Q_3$ | | 52.65 (2.44) | 52.68 (2.66) | 52.61 (2.70) | 52.75 (2.62) | 52.65 (2.72) |
| | | $Q_4$ | | 62.85 (2.47) | 62.83 (2.75) | 62.63 (2.67) | 62.88 (2.72) | 62.58 (2.68) |
| | Estimated additive effect | $Q_1$ | 1.00 (0.17) | | 1.10 (0.20) | 1.11 (0.21) | 23.32 (4.10) | 0.06 (0.01) |
| | | $Q_2$ | 1.01 (0.18) | | 1.09 (0.21) | 1.11 (0.20) | 23.42 (4.52) | 0.06 (0.01) |
| | | $Q_3$ | | 1.00 (0.19) | 1.11 (0.20) | −1.11 (0.22) | 26.46 (4.96) | −0.07 (0.01) |
| | | $Q_4$ | | 1.00 (0.18) | 1.10 (0.20) | −1.12 (0.21) | 26.61 (4.82) | −0.07 (0.01) |
| B | Power (%) | $Q_1$ | 95.40 | | 67.40 | 65.60 | 54.80 | 49.90 |
| | | $Q_2$ | 92.90 | | 62.40 | 66.00 | 50.00 | 49.90 |
| | | $Q_3$ | | 93.70 | 69.90 | 67.00 | 79.20 | 74.90 |
| | | $Q_4$ | | 91.90 | 62.40 | 64.90 | 73.50 | 72.90 |
| | FDR (%) | | 21.35 | 22.18 | 28.76 | 28.59 | 28.07 | 28.89 |
| | Estimated position (cM) | $Q_1$ | 18.46 (2.27) | | 18.43 (2.57) | 18.66 (2.51) | 18.51 (2.72) | 18.73 (2.54) |
| | | $Q_2$ | 52.80 (2.39) | | 52.63 (2.71) | 52.43 (2.69) | 52.48 (2.71) | 52.39 (2.70) |
| | | $Q_3$ | | 28.49 (2.24) | 28.52 (2.54) | 28.64 (2.50) | 28.60 (2.60) | 28.70 (2.36) |
| | | $Q_4$ | | 62.86 (2.48) | 62.75 (2.77) | 62.46 (2.68) | 62.79 (2.74) | 62.52 (2.70) |
| | Estimated additive effect | $Q_1$ | 1.01 (0.19) | | 1.16 (0.24) | 1.15 (0.24) | 25.40 (4.94) | 0.07 (0.01) |
| | | $Q_2$ | 1.01 (0.19) | | 1.16 (0.25) | 1.16 (0.23) | 25.12 (5.63) | 0.07 (0.01) |
| | | $Q_3$ | | 1.03 (0.19) | 1.15 (0.23) | −1.16 (0.24) | 27.47 (5.48) | −0.07 (0.01) |
| | | $Q_4$ | | 1.00 (0.18) | 1.12 (0.23) | −1.14 (0.22) | 26.61 (5.40) | −0.07 (0.01) |
| C | Power (%) | $Q_1$ | 95.20 | | 66.60 | 52.40 | 53.60 | 37.70 |
| | | $Q_2$ | 95.00 | | 69.20 | 51.60 | 54.70 | 36.40 |
| | | $Q_3$ | | 92.90 | 63.40 | 47.80 | 69.70 | 56.20 |
| | | $Q_4$ | | 92.60 | 61.50 | 49.90 | 72.60 | 58.00 |
| | FDR (%) | | 19.78 | 23.44 | 28.83 | 27.71 | 29.74 | 30.18 |
| | Estimated position (cM) | $Q_1$ | 18.51 (2.32) | | 18.45 (2.53) | 18.47 (2.59) | 18.50 (2.60) | 18.40 (2.62) |
| | | $Q_2$ | 28.45 (2.25) | | 28.55 (2.55) | 28.44 (2.44) | 28.61 (2.62) | 28.56 (2.45) |
| | | $Q_3$ | | 52.83 (2.36) | 52.62 (2.72) | 52.66 (2.73) | 52.60 (2.66) | 52.65 (2.68) |
| | | $Q_4$ | | 62.82 (2.40) | 62.69 (2.75) | 62.75 (2.83) | 62.71 (2.74) | 62.83 (2.79) |
| | Estimated additive effect | $Q_1$ | 1.00 (0.17) | | 1.16 (0.23) | 1.12 (0.21) | 24.76 (4.74) | 0.06 (0.01) |
| | | $Q_2$ | 1.01 (0.17) | | 1.16 (0.23) | 1.12 (0.21) | 24.88 (4.72) | 0.06 (0.01) |
| | | $Q_3$ | | 0.99 (0.18) | 1.16 (0.25) | −1.12 (0.21) | 27.88 (6.22) | −0.07 (0.01) |
| | | $Q_4$ | | 0.99 (0.17) | 1.12 (0.23) | −1.11 (0.21) | 27.17 (5.76) | −0.07 (0.01) |

Values in brackets are standard errors

QTL (denoted by qZ1–qZ11, where q stands for QTL and Z for *Zea mays* L.) were found to be distributed on eight of the ten maize chromosomes (Table S5; Fig. 3). qZ1 and qZ2 were located on chromosome 1; qZ3, qZ4, and qZ5 were located on chromosome 2; and the other six QTL were located on different

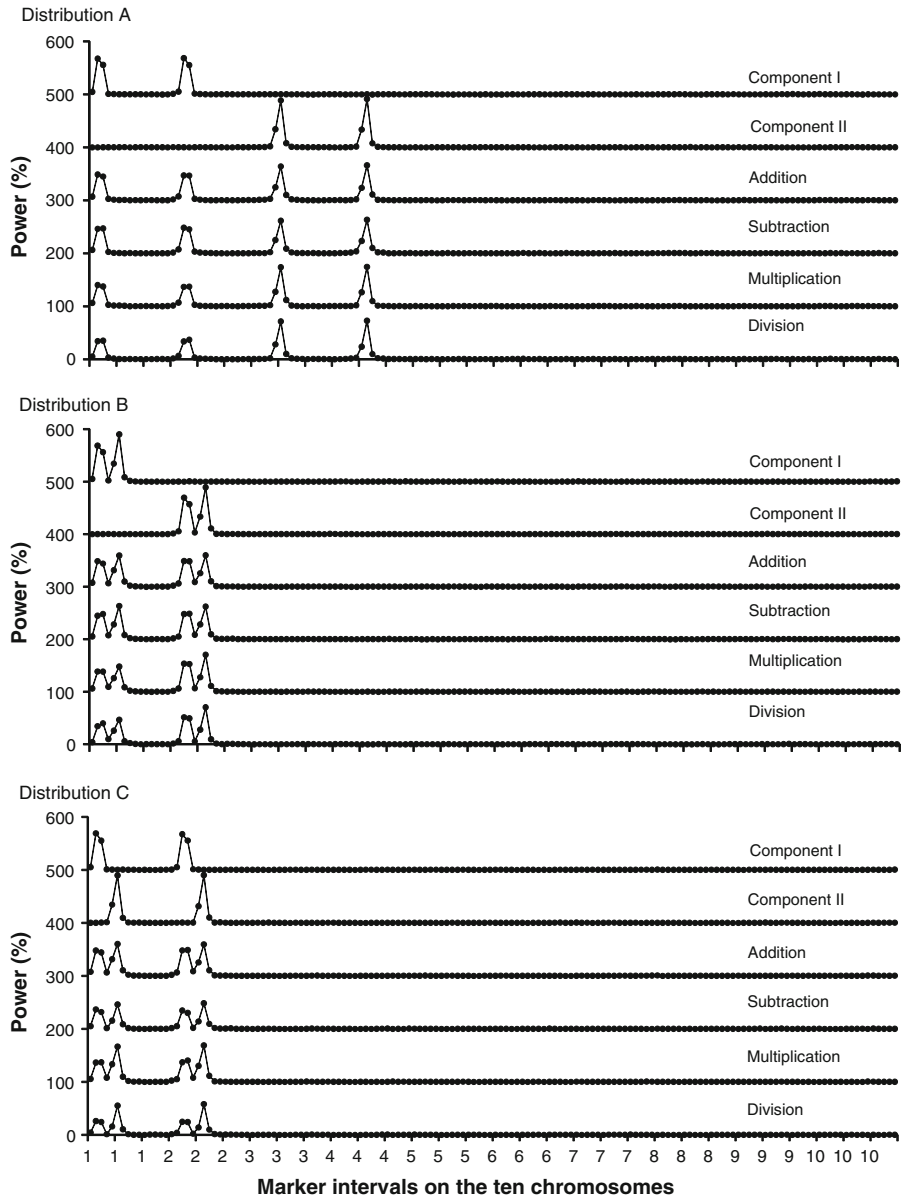


**Fig. 2** QTL detection power of the pure additive genetic model, i.e., Effect A, for the three QTL distribution models. Power was calculated as the proportion of simulated populations where one QTL was located in each of the 150 marker intervals defined by 160 markers on the ten chromosomes. Each interval was defined by two flanking markers. For clarity, 100, 200, 300, 400, and 500 were added to the detection power of multiplication, subtraction, addition, component trait II, and component trait I, respectively

chromosomes. Seven QTL control component I, explaining 59.14% of the phenotypic variance, and seven QTL control component II as well, explaining 60.35% of the phenotypic variance. Three unlinked QTL (i.e., qZ4, qZ10, and qZ11) control the two component traits simultaneously, and their effects were in the same direction (Table S5), which is understandable considering the significant positive correlation between components I and II (Fig. 1). In addition, qZ3, qZ6, and qZ11 each explained more than 10% of the phenotypic variance of component I, as did qZ4 and qZ11 for component II. Thus qZ3, qZ4, qZ6, and qZ11 can be viewed as major QTL for the two component traits.

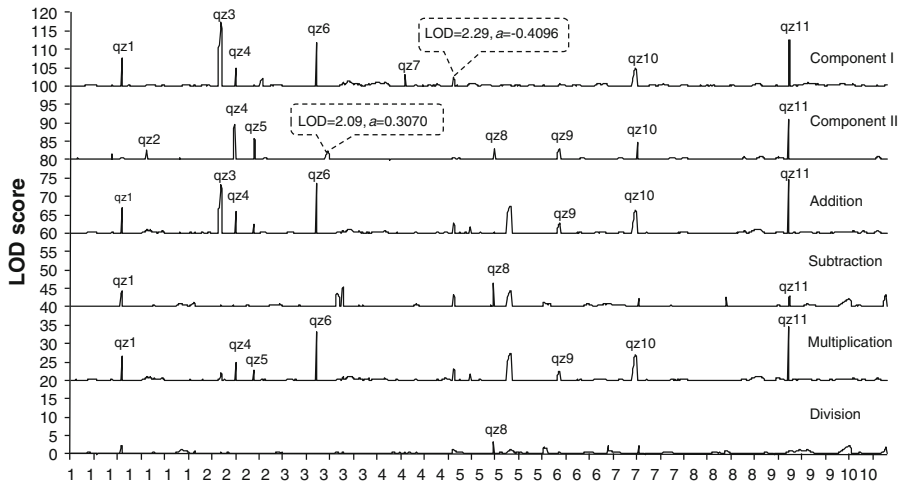


**Fig. 3** LOD score profiles from one-dimensional scanning for two component traits and four derived traits in a maize RIL population. For clarity, 20, 40, 60, 80, and 100 were added to the LOD scores of multiplication, subtraction, addition, component trait II, and component trait I, respectively

For derived trait addition, the four major QTL mentioned above were all detected, but four of the 11 QTL were not identified, i.e., qZ2, qZ5, qZ7, and qZ8 (Table S5, Fig. 3). Two QTL were located on chromosome 5 in the repulsion phase, at a distance of 97 cM apart. As for the seven QTL that were correctly identified for addition, their position estimates were similar to those of the two components, but their effects were over-estimated about two-fold compared with the estimates of component traits (Table S5). For subtraction, most of the 11 QTL were not identified. Only one major QTL (i.e., qZ11) was detected with unbiased position estimation. Instead, five additional positives were located on chromosomes 3, 5, and 10. For multiplication, the number of identified QTL and the two new positives were the same as those for addition, except that one major QTL, i.e., qZ3, was not detected. Results for division were the worst. Only one QTL, i.e., qZ8, was detected. None of the four major QTL was detected for division (Table S5).

In order to choose the putative genetic models of the following simulations, qZ4, qZ10, and qZ11 were assigned pleiotropic effects on the two components. In fact, qZ4 was identified at the same chromosomal position, i.e., 77 cM on chromosome 2, for both component traits, and this position was used in simulation. qZ10 was mapped at 46 cM and 49 cM on chromosome 7 for the two components, respectively, and position 47 cM was used in simulation. qZ11 was mapped at 42 cM and 40 cM on chromosome 9 for the two components, respectively, and position 40 cM was used in simulation.

## Power simulation in the QTL distribution and effect model identified in the maize RIL population

When component I was used in QTL mapping, the detection power of the four major QTL, i.e., qZ1, qZ3, qZ6, and qZ11, was greater than 80% (Table S6) due to their large genetic effects (Table S5). The power of qZ4 was lower than that of qZ3 (Table S6) because qZ4 is linked to qZ3 on chromosome 2, and the additive effect of qZ4 was smaller compared with qZ3 (Table S5). As expected, qZ7 had the smallest effect among the seven QTL for trait I (Table S5), and so had the lowest detection power (Table S6). Similarly, qZ4, qZ5, qZ10, and qZ11 were the top four QTL controlling component II, and their detection power was greater than 85% (Table S6). qZ2 was the smallest QTL of the seven QTL controlling component II (Table S5), and its detection power was the lowest, i.e., 53.5% (Table S6). In addition, the FDR for the two component traits was around 23.0%.

In general, when derived traits were used, QTL detected for both component and derived traits had comparable power; however, those detected for component traits but not for derived traits had low detection power (Table S6). For example, qZ2, qZ5, qZ7, and qZ8 were not detected for addition (Table S5), and their detection power was 12.3, 47.2, 25.8, and 19.7%, respectively (Table S6), which is much lower than those for components I and II. qZ8 and qZ9 were detected in the actual population for component II, and explained 2.93 and 2.88%,

respectively, of the phenotypic variance for component II. They had medium–high detection power when component II was used in simulated populations, i.e., 70.0 and 64.0%, respectively, but very low detection power when derived traits were used, i.e., 13.7–21.7%.

On the other hand, most QTL with high detection power for derived traits were detected in the actual population for the corresponding derived traits (Tables S5 and S6). However, the power of qZ3 was 97.0, 98.4, 96.7, and 98.3% for addition, subtraction, multiplication, and division, respectively (Table S6), but qZ3 was only detected for addition in the actual maize population (Table S5), possibly due to the increase in QTL number and genetic complexity. As for the two component traits, there were seven additive QTL in their genetic model (three QTL were simulated as pleiotropic; Table S6). Eleven additive QTL were involved in addition and subtraction. For multiplication and division, there must be digenic and higher-order interactions between the 11 QTL (Tables S2 and S3), which reduced the efficiency of additive QTL mapping.

The FDR for subtraction and division were much higher than the FDR for the two component traits, and derived traits addition and multiplication (Table S6), which may also explain the fact that several additional QTL were identified for subtraction in the actual mapping population. Similar to the three putative genetic models, QTL position was almost unbiased for both component and derived traits (Tables S5 and S6). The effect was over-estimated for the two component traits, and under-estimated for derived traits (Tables 3, S5 and S6).

## Heritability of component and derived traits

For simulated Effect A, heritabilities of the four derived traits were equal to or lower than those for the two component traits in Distributions A and B (Table S7). In Distribution C, heritabilities of addition and multiplication were higher than those of subtraction and division, since the linkage phase is present in different derived traits (Table S7). Linkage in coupling, as present in addition and multiplication, increases the genetic variance, and therefore increases heritability as well. On the contrary, linkage in repulsion, as present in subtraction and division, decreases the genetic variance, and therefore decreases heritability. Heritability in the other two QTL distribution and effect models in the maize population follows a similar trend, except that the change in genetic variance is also caused by pleiotropic QTL in the maize population. Even if derived traits have similar heritability to that of component traits, more QTL are involved in the genetic architecture of derived traits, and these QTL have more complicated linkage relationship and genetic effects. It is expected that the use of derived traits will result in reduced power and increased false positives.

## What does a derived-only QTL stand for?

Some derived-only QTL have been reported that were identified for a derived trait but not for either of the two component traits. This happened in the maize population used in this study as well. Two linked QTL on chromosome 3 and one QTL on chromosome 10 were identified for subtraction. Two QTL at 1 and 98 cM on chromosome 5, respectively, were identified for addition, subtraction, and multiplication, but none of them was identified for either component trait (Table S5). However, some derived-only QTL may be explained by less-significant QTL in component traits. For example, there was a peak in the LOD profile of component I at 1 cM of chromosome 5, where the LOD score was 2.29, and the additive effect was −0.4096 (see dashed-line box in Fig. 3). No clear peak was observed in the LOD profile of component II around this position, so its effect on component II can be regarded as 0. It is to be expected that if this QTL could be identified for addition, subtraction, and multiplication, it would have negative effects as well. In reality, its effect was estimated as −0.7590, −0.3084, and −67.0759 for addition, subtraction, and multiplication, respectively (Table S5). Though it does not exceed the LOD threshold of 2.5, this QTL is very likely to be the same as those identified at this position for addition, subtraction, and multiplication. Two linked QTL on chromosome 3 identified for subtraction may be the same as the one in the peak having a LOD score of 2.09 for component II (see dashed-line box in Fig. 3). However, the QTL identified for three derived traits at 98 cM on chromosome 5 is an exception (Fig. 3). There were no clear peaks in the LOD profiles of traits I and II around position 98 cM on chromosome 5.

To investigate the distribution of significant QTL (including true and false positives) in the genome, detection power was calculated for marker intervals defined by 756 markers on the maize genome, i.e., each interval defined by two flanking markers was viewed as a support interval (Fig. S2). No significant QTL was located on chromosomes 8 and 10 through QTL mapping for the two component traits (Table S5); therefore, no QTL was assumed on them in simulation. As a result, the probability that a QTL was mapped on the two blank chromosomes was close to 0 (Fig. S2), regardless of whether component or derived traits were used. In putative effect models Effect A and Effect B under Distributions A–C, we did not observe high detection power in chromosome regions other than the four predefined QTL (Figs. 2, and S1), indicating the additive QTL identified from derived traits must be QTL identified for one component trait or for multiple component traits. In Effect C, no chromosomal regions showed significantly high frequency of additive QTL when using the four derived traits in QTL mapping (Fig. S3), indicating that epistasis between QTL controlling component traits is less likely to cause the derived-only additive QTL. Thus, if a chromosome does not harbor any additive QTL affecting component traits, it is unlikely that any additive QTL will be identified for a derived trait.

High detection power was observed only around the 11 identified QTL, indicating that derived-only QTL may be false positives. Low power was observed for qZ8 and qZ9 for derived traits, due to their small additive effects on component II (Table S5). Both qZ10 and qZ11 had high detection power for the two component traits addition and multiplication, but had close to zero detection power for subtraction and division. This is understandable when looking at their genetic effects on the two component traits. The additive effect of qZ10 was estimated as −0.5835 and −0.4757 on components I and II, respectively. The additive effect of qZ11 was estimated as 0.9959 and 0.7396 on components I and II, respectively. They will have much larger effects on addition and multiplication, but much smaller effects on subtraction and division. Thus qZ10 and qZ11 can be easily identified for addition and multiplication (Table S6; Fig. S2), but not for subtraction and division. When a derived trait is used, some QTL may have detection power comparable to that of component traits (e.g., qZ1, qZ3, and qZ6 in each derived trait), while some may have lower detection power, e.g., qZ10 and qZ11 in subtraction or division (Table S6; Fig. S2). For the two component traits, high detection power was observed around all the 11 QTL positions, and no clear high detection power was observed beyond the 11 QTL identified in the actual maize population. In summary, derived-only QTL can be explained either as minor QTL that are not significant in QTL mapping of component traits, or as false positives.

## Discussion

Derived traits have been frequently used in genetics and breeding. When used in QTL mapping, they often show discrepancy with QTL identified for component traits, and derived-only QTL have occasionally been reported. In this study we show that the genetic control of derived traits can be very complicated, even when a simple genetic model was assumed for component traits, especially for multiplication and division (Tables S2, S3, and S4). The complexity arises from three sources: (1) the number of QTL involved, (2) higher-order QTL interaction, and (3) the linkage relationship between QTL.

Each QTL that affects a component trait may affect a derived trait as well. So the number of QTL affecting a derived trait is greater than the number of QTL affecting each component trait. For the two component traits defined in Table 1 and the pure additive effect model (Table 2), derived traits multiplication and division contain interacting genetic effects (Table S2). The increase in the number of QTL will reduce the efficiency of QTL mapping due to the decreased proportion of the phenotypic variance for each QTL that can be explained (Table S3) and the increased difficulty in controlling the background genetic variance (Li et al. 2007; Zhang et al. 2008). Interacting effects or epistasis will greatly complicate the QTL mapping procedure if epistatic effects are to be included and estimated (Li et al. 2008; Wang 2009). Derived traits may also complicate the linkage relationship between QTL. Taking Distribution C and Effect A as an example (Tables 1 and 2), $Q_1$ and $Q_3$ were linked on chromosome 1, and $Q_2$ and $Q_4$ were linked on chromosome 2. Each component trait was controlled by two independent QTL, and therefore detection power was high when

component traits were used in QTL mapping (Table 3). In comparison, each derived trait was controlled by two pairs of linked QTL. Linkage was involved in the genetic control of each derived trait, and therefore reduced QTL detection power (Table 3).

The increased complexity of the genetic control of a derived trait also complicates the calculation of genetic variance and heritability (Tables S3 and S4). Taking Effect A as an example, when the QTL for one component trait are independent from the QTL for another component trait, i.e., Distributions A and B, the variance of addition or subtraction is equal to the sum of the variances of two component traits. For Distribution C, the genetic variance of addition or subtraction is not equal to the sum of the two component traits due to the linkage between $Q_1$ and $Q_3$ and between $Q_2$ and $Q_4$. For addition, $Q_1$ and $Q_3$ are linked in the coupling phase. This holds true for $Q_2$ and $Q_4$ as well. The coupling linkage increases the genetic variance of addition (Table S3). For subtraction, $Q_1$ and $Q_3$ are linked in the repulsion phase. The same is true for $Q_2$ and $Q_4$. The repulsive linkage decreases the genetic variance of addition (Table S3), and the change in genetic variance reflects the change in heritability. In Distributions A and B, heritability of derived traits is comparable to that of component traits, whereas in Distribution C, subtraction and division have much lower heritability (Table S7). In the distribution and effect model from the maize population, the low heritability of subtraction and division may also be caused by positive pleiotropic QTL, i.e., QTL having the same effect direction on both component traits.

Genetic variance and environmental error together determine broad-sense heritability. Genetic variance of multiplication or division can be calculated from genotypic values of the 16 genotypes (Table S1) and their expected frequencies in a RIL population, but the environmental error is difficult to obtain theoretically. In simulation, we can separate genetic effects from environmental effects, and thus are able to calculate the heritability for all traits (Table S7). After logarithmic transformation, multiplication can be viewed as the addition of two component traits, and division can be viewed as the subtraction of two component traits. Therefore, multiplication has similar heritability to addition, and division has similar heritability to subtraction. In the maize population, QTL detected for addition and multiplication are more common, as are QTL detected for division and subtraction, but the LOD score for division is much lower (Table S5). In simulation, QTL detection powers for multiplication and addition are more similar, as are QTL detection powers for division and subtraction. Similar simulation results were obtained when two epistatic effects between $Q_1$ and $Q_2$ and between $Q_3$ and $Q_4$ were included (i.e., Effect B) in Distributions A–C (Tables S3 and S4).

In the actual maize genetic population, we understand that the other three derived traits, i.e., addition, multiplication, and division of FFLW and MFLW in the maize population, may not have meaningful biological background. Instead of using more populations where each derived trait has a biological background, we simply used all four derived traits from FFLW and MFLW to show the difference in QTL mapping results. Although not reported in this study, we tried one rice $F_2$ population phenotyped for grain length and grain width (where division makes sense), and one maize RIL population phenotyped for two protein contents (where addition makes sense). Very similar results were obtained in these two mapping populations as well.

Taking ASI as an example, we believe that a QTL has an effect on ASI only if it has an effect on FFLW but not on MFLW (i.e., qZ1, qZ3, qZ6, and qZ7 in Table S5), or if it has an effect on MFLW but not on FFLW (i.e., qZ2, qZ5, qZ8, and qZ9 in Table S5), or it has an effect on FFLW and MFLW but the effects are of different sizes (i.e., qZ4, qZ10, and qZ11 in Table S5). We do not exclude the possibility that some QTL may become easier to detect for ASI. For example, if one QTL has an effect of 0.5 day on FFLW, but an effect of −0.5 day on MFLW, it will have an effect of 1 day on ASI. If this is the case, this QTL may become easier to locate through ASI. In the marker-interval power analysis based on the observed QTL distribution and effect model in the maize population (Fig. S3), except for those around the 11 identified QTL we did not see other chromosomal positions that had abnormally high power for FFLW and MFLW. The two ASI-only QTL (identified at 98 cM on chromosome 5 and 91 cM on chromosome 10; Table S5) were much likely false positives, as no significant peaks were observed in similar regions of the LOD profiles of FFLW and MFLW.

In breeding, index selection is commonly used to combine all the information available on each component's performance (Baker 1986; Falconer and

Mackay 1996; Bernardo 2002). Though different indices, such as optimum index, base index, and multiplicative index, etc. (Baker 1986; Bernardo 2002) have been proposed, typically most are derived traits and may have much more complicated genetic architecture than component traits. Few genetic studies have been conducted based on indices, but this does not deter their use in breeding. In fact, genetic studies and breeding have objectives that are different, but not mutually contradictory in the broad sense. It is the breeders' objective to combine as many favorable genes as possible. The use of derived traits is efficient for selecting all favorable genes simultaneously. In contrast, geneticists have the objective of studying as many component genes as possible. For this purpose, the use of component traits may be more efficient, since fewer genes are involved.

In conclusion, the use of derived traits in QTL mapping may increase the QTL number; may decrease the proportion of phenotypic variance that can be explained by component QTL; may cause higher-order QTL interactions than observed in component traits; and may complicate the linkage relationship between QTL. The increased complexity of the genetic architecture of derived traits reduces QTL detection, and increases the false discovery rate. However, this should not rule out the use of derived traits as indices in breeding where the simultaneously selecting multiple genes is the major objective.

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