Identification of Heading Date Quantitative Trait Locus *Hd6* and Characterization of Its Epistatic Interactions With *Hd2* in Rice Using Advanced Backcross Progeny

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ABSTRACT

A backcrossed population (BC_4F_2) derived from a cross between a *japonica* rice variety, Nipponbare, as the recurrent parent and an *indica* rice variety, Kasalath, as the donor parent showed a long-range variation in days to heading. Quantitative trait loci (QTL) analysis revealed that two QTL, one on chromosome *3*, designated *Hd6*, and another on chromosome *2*, designated *Hd7*, were involved in this variation; and *Hd6* was precisely mapped as a single Mendelian factor by using progeny testing (BC_4F_3). The nearly isogenic line with QTL (QTL-NIL) that carries the chromosomal segment from Kasalath for the *Hd6* region in Nipponbare's genetic background was developed by marker-assisted selection. In a day-length treatment test, the QTL-NIL for *Hd6* prominently increased days to heading under a 13.5-hr day length compared with the recurrent parent, Nipponbare, suggesting that *Hd6* controls photoperiod sensitivity. QTL analysis of the F_2 population derived from a cross between the QTL-NILs revealed existence of an epistatic interaction between *Hd2*, which is one of the photoperiod sensitivity genes detected in a previous analysis, and *Hd6*. The day-length treatment tests of these QTL-NILs, including the line introgressing both *Hd2* and *Hd6*, also indicated an epistatic interaction for photoperiod sensitivity between them.

THE genetic analysis of quantitative traits using DNA markers is a landmark feature in the field of plant genetics. Since the first application of DNA markers to quantitative trait loci (QTL) mapping in tomato was reported (Paterson *et al.* 1988), numerous genetic studies of quantitative traits have been done in a large number of plant species. Some QTL were suggested to be associated with some major genes previously identified by classical genetic analysis (Beavis *et al.* 1991; Yano *et al.* 1997). Syntenic relationships in chromosomal constitution involving QTL among plant species were also suggested from the results of comparative linkage mapping among different plant species with common DNA markers (Paterson *et al.* 1995).

Although QTL analysis gives us much information on plant genetics, it has inherent methodological problems, especially in QTL detection. First, it is difficult to distinguish two QTL that are tightly linked. Second, which threshold should we use to detect QTL with relatively small effect? Third, how do we detect a QTL showing epistatic interaction with other QTL (Tanksley 1993; Yano and Sasaki 1997)? Developments in statistical genetics and improvements in analytical software have contributed to solving these problems (Tinker and Mather 1995; Chase *et al.* 1997; Nelson 1997).

Several attempts to identify epistatic interactions among QTL have been made, including successful studies of soybean (Lark *et al.* 1995) and rice (Li *et al.* 1997; Yu *et al.* 1997). However, confidence in their detection of interactions is low because of small population size or the use of primary segregating populations such as F_2, F_2-derived F_3, or recombinant inbred lines that segregate whole parental chromosomal segments simultaneously. To improve confidence, different types of plant materials have been constructed. Series of chromosomal substitution lines or nearly isogenic lines (NILs) with QTL (QTL-NILs) have been developed, and the gene actions of QTL have been analyzed in detail (Dorweiler *et al.* 1993; Doebley *et al.* 1995; Eshed and Zamir 1996; Tanksley *et al.* 1996; Bernacchi and Tanksley 1997; H. X. Lin, T. Yamamoto, T. Sasaki and M. Yano, unpublished results). Moreover, fine mapping of QTL has been done by using QTL-NILs (Alpert and Tanksley 1996; Yamamoto *et al.* 1998) to clone them, which suggests that some QTL can be dealt with as Mendelian factors.

Heading date is a critical trait for adaptation to different cultivation areas and cropping seasons. At present, 23 major genes controlling heading date have been reported in rice, and 13 of them were determined for

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localized chromosome (Ichitani *et al.* 1998; Kinoshita 1998). On the other hand, many reports of QTL mapping for heading date in rice by using DNA markers have also increased in these 5 years (Li *et al.* 1995; H. X. Lin *et al.* 1995; Xiao *et al.* 1995, 1996, 1998; Lu *et al.* 1997; Yano *et al.* 1997; Doi *et al.* 1998; S. Y. Lin *et al.* 1998; Xiong *et al.* 1999). It is necessary to clarify the relationships among these major genes and QTL, and their biological functions—response to photoperiod and duration of basic vegetative growth.

Yano *et al.* (1997) has reported five QTL, designated *Hd1–Hd5*, controlling rice heading date in an F_2 population from a cross between a *japonica* variety, Nipponbare, and an *indica* variety, Kasalath. Another three QTL have been reported based on the analysis of backcross inbred lines derived from the same cross (Lin *et al.* 1998). These reports implied that the detected QTL could not explain all of the variation in days to heading. In this study, an unpredictable long-range variation in days to heading was observed in a population derived from one backcrossed plant homozygous for the Nipponbare allele in seven of eight known QTL and heterozygous in the other. To identify genetic factors involving this variation, QTL analysis of heading date in this population was done. We then tried to confirm this newly found QTL as a Mendelian factor by the method of fine mapping used by Yamamoto *et al.* (1998). Subsequently, a day-length treatment test was done by using some combinations of QTL-NILs and their recurrent parent for estimating the gene action of this QTL. We discuss why we could detect this QTL in the backcrossed population but not in the F_2 population, and the possibility of epistatic interaction among QTL controlling heading date.

MATERIALS AND METHODS

Experimental materials: The process of developing experimental material followed Yamamoto *et al.* (1998). An F_1 plant, a cross between Nipponbare and Kasalath, was backcrossed with Nipponbare as the male parent. By self-pollinating of this BC_1F_1 plant, several BC_1F_2 populations were produced. Suitable BC_1F_2 plants, in which at least five QTL for heading date (*Hd1–Hd5*; Yano *et al.* 1997) were homozygous for the Nipponbare allele, were selected by whole-genome survey with restriction fragment length polymorphism (RFLP) markers and crossed with Nipponbare again. Finally, we selected a BC_4F_1 plant (BC_4F_1-37-7), in which there were introgressed chromosomal segments of parts of chromosomes *2*, *3*, *6*, and *8* from Kasalath (Figure 1).

Self-pollinated progeny (BC_4F_2) derived from BC_4F_1-37-7 ($n = 100$) were cultivated in an experimental paddy field at the National Institute of Agrobiological Resources, Tsukuba, Japan. Scoring of days to heading (defined as duration from sowing to emergence of the first panicle) and RFLP analysis for heterozygous chromosomal regions were done for all segregants. Then 50 BC_4F_3 progeny of each BC_4F_2 plant were cultivated in the paddy field. The genotype of the target QTL in each BC_4F_2 plant was determined from the segregation of days to heading in the progeny lines. BC_4F_2 and BC_4F_3 progeny were cultivated in the normal growing season according to standard practice. The duration from seeding to heading was from April to August. The mean day lengths and mean temperatures under natural conditions in Tsukuba are as follows: 12 hr, 56 min and 14.3° for April; 14 hr, 4 min and 18.7° for May; 14 hr, 37 min and 19.8° for June; 14 hr, 17 min and 23.5° for July; and 13 hr, 26 min and 25.2° for August, respectively.

Linkage mapping and QTL analysis: To make RFLP linkage maps for the heterozygous regions of BC_4F_1-37-7, 26 RFLP markers in these regions were selected from a high-density linkage map constructed by Harushima *et al.* (1998). The genotypes of these loci in each BC_4F_2 plant were determined by Southern hybridization analysis following the procedure of Kurata *et al.* (1994).

Mapmaker/EXP 3.0 (Lander *et al.* 1987) was used for linkage analyses based on the genotype data of each BC_4F_2 plant. The Kosambi function was used to calculate genetic distances. QTL for heading date were estimated by Mapmaker/QTL 1.1 (Lincoln *et al.* 1993). Putative QTL were identified in regions exceeding 3.0 LOD (log likelihood value). Fine mapping of target QTL was done by using genotype data of target QTL estimated in BC_4F_3 progeny testing.

Evaluation of gene action and confirmation of epistatic interaction of QTL: To evaluate the gene action of target QTL, a day-length treatment test was done. A QTL-NIL in which a chromosomal region of the target QTL was homozygous for the Kasalath allele was selected by marker-assisted selection (MAS) from the segregants of a series of backcrossed progeny. This QTL-NIL, called NIL(*target QTL*), and Nipponbare as a control were cultivated under four day-length conditions (10.5, 12.0, 13.5, and 14.5 hr) in growth chambers. The trial used a completely randomized design with two replications per block, seven plants per replication. Days to heading of each plant were scored as in the field experiment.

A preliminary experiment using some backcross progeny suggested that the response to photoperiod of *Hd2*, a photoperiod sensitivity gene (H. X. Lin, T. Yamamoto, T. Sasaki and M. Yano, unpublished results), seemed to be affected by the genotype of the target QTL newly found in this study. To confirm the epistatic interaction of *Hd2* and the target QTL, self-pollinated progeny of an F_1 plant derived from a cross between NIL(*Hd2*), developed by our group (H. X. Lin, T. Yamamoto, T. Sasaki and M. Yano, unpublished results), and NIL(*target QTL*) were cultivated in the paddy field. Scoring of days to heading and RFLP analysis were done for all segregants. The genotype of each QTL was assigned to the genotype of the marker locus nearest to it. Averages of days to heading in each class of QTL combination were compared by SAS GLM Proc (SAS Institute 1989).

Selected lines of three kinds of QTL-NILs—NIL(*Hd2*), NIL(*target QTL*), and NIL(*Hd2*/*target QTL*), in which both *Hd2* and the target QTL are introgressed—and Nipponbare were cultivated under three day-length conditions (10.5, 12.0, and 14.5 hr) in growth chambers. The days to heading in each line were then compared among lines. The same experimental design as above was used.

RESULTS

Frequency distribution of days to heading and QTL analysis in the BC_4F_2 population: The selected plant, BC_4F_1-37-7 (Figure 1), was homozygous for the Nipponbare alleles for five QTL (*Hd1–Hd5*) detected in the F_2 population (Yano *et al.* 1997). This plant was also homozygous for two of three additional QTL detected in backcross inbred lines of the same parents and het-

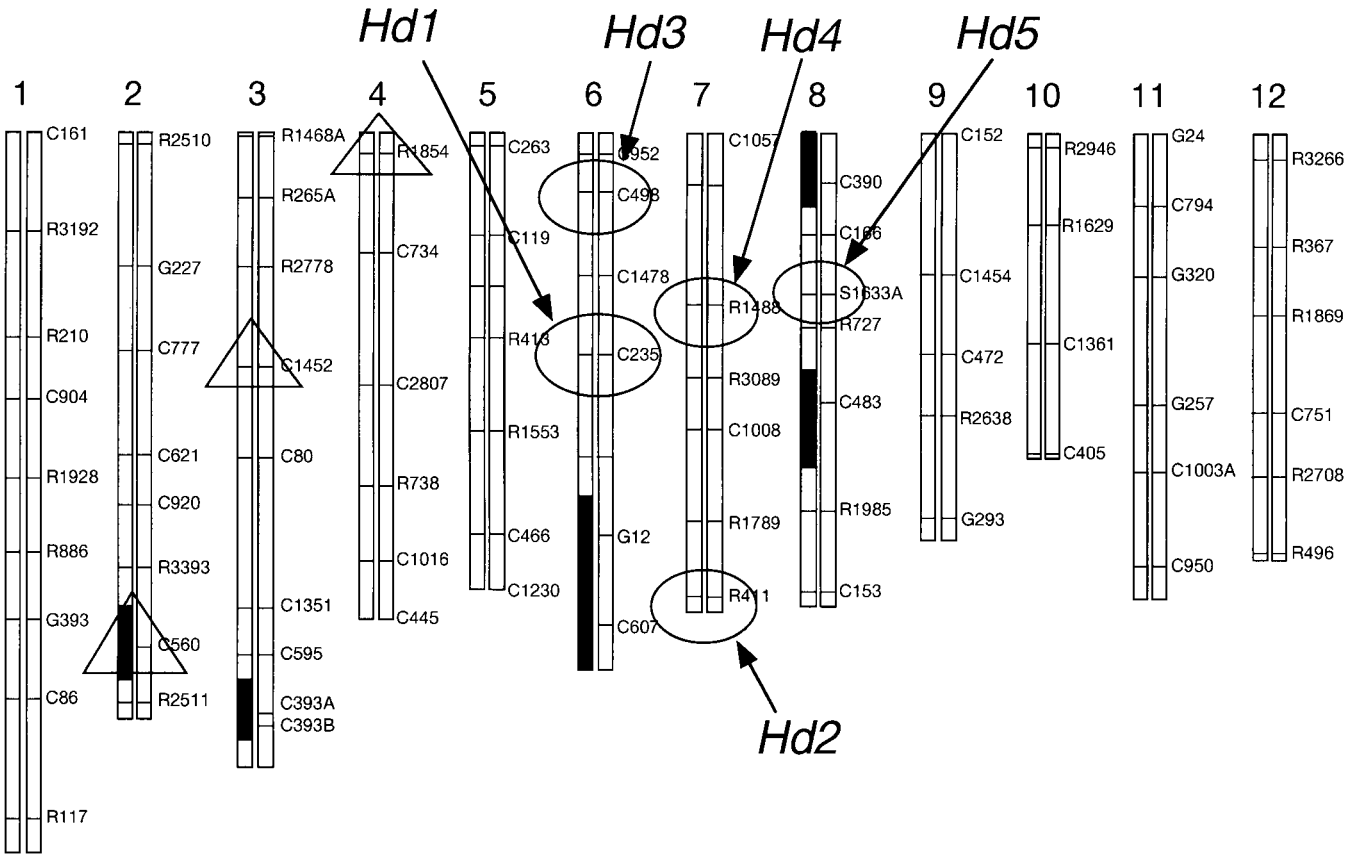

Figure 1.—Graphical genotype of plant BC_4F_1-37-7. Black and white regions represent segments of the chromosomes derived from Kasalath and Nipponbare, respectively. Ellipses indicate approximate positions of QTL detected in the F_2 population (Yano *et al.* 1997); triangles indicate three additional QTL detected in a BC_1F_5 population (Lin *et al.* 1998).

erozygous for the other on chromosome *2* (Lin *et al.* 1998). A self-pollinated progeny derived from this plant showed a continuous variation of 22 days' range (Figure 2). This variation seemed to be later than the variation in Nipponbare. QTL analysis with genotype data of the heterozygous regions of BC_4F_1-37-7 revealed that the most significant QTL (tentatively designated *Hd6*) was near RFLP marker R3226 on the long arm of chromosome *3* (Table 1). Another QTL (tentatively designated *Hd7*) showing a significant signal was near RFLP marker C560 on chromosome *2* (Table 1). We thus identified a QTL, *Hd6*, that had escaped from the QTL detection in a previous F_2-based analysis by Yano *et al.* (1997) and confirmed another, *Hd7*, which is likely to be the QTL detected by Lin *et al.* (1998).

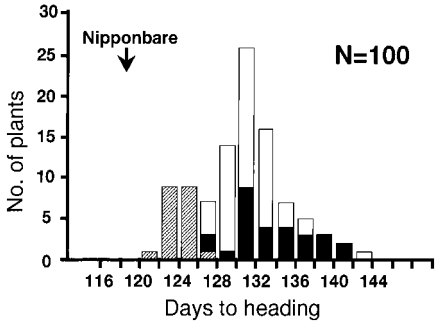

Figure 2.—Frequency distribution of days to heading in self-pollinated progeny derived from BC_4F_1-37-7. Three genotype classes of *Hd6*, (□) heterozygous, (■) homozygous for Kasalath allele, and (▨) homozygous for Nipponbare allele, were estimated by BC_4F_3 progeny tests.

Fine mapping of *Hd6*: In BC_4F_3 progeny testing, three apparent phenotypes of heading were clearly visible: fixed lines of early heading (20 lines), segregating lines from early to late (52), and fixed lines of late heading (28). These values fit the ratio of single Mendelian segregation ($\chi^2 = 1.44$). The three phenotypes were likely caused by the differences in the *Hd6* genotypes, based on the comparison of explained variances between *Hd6* and *Hd7*, although these two QTL segregated simultaneously in this population. Thus, early fixed lines are likely to be homozygous for the Nipponbare allele at *Hd6*, segregating lines are likely to be heterozygous, and late fixed lines are likely to be homozygous for the Kasalath allele. No recombinant was observed between *Hd6* and five RFLP markers, R2443, C217, R2404, R2311, and R2632 (Figure 3). This position was slightly different from the LOD peak of the QTL analysis (R3226).

Characterization of *Hd6*: Figure 4A shows a graphical

TABLE 1

QTL controlling heading date detected in a self-pollinated population derived from BC_4F_1-37-7

QTL	Chromosome	NML	LOD	Effects on the phenotype			
				a	*d*	*d*/*a*	PVE
Hd6	*3*	R3226	19.2	4.8	2.5	0.52	58.7
Hd7	*2*	C560	3.2	2.4	0.1	0.04	13.8

NML, nearest marker locus to the QTL; LOD, log likelihood value calculated by MAPMAKER/QTL vers. 1.1 in the condition of unconstrained genetics; *a*, additive effect on the Kasalath allele on days to heading; *d*, dominant effect of the Kasalath allele; *d*/*a*, degree of dominance; PVE, percentage of total phenotypic variance explained by the QTL.

genotype of NIL(*Hd6*). Table 2 shows days to heading in NIL(*Hd6*) and Nipponbare under different day lengths. There was a significant difference in photoperiod sensitivity between NIL(*Hd6*) and Nipponbare at 13.5-hr day length, suggesting that *Hd6* was the locus controlling photoperiod sensitivity and that the Kasalath allele enhanced photoperiod sensitivity.

Evidence for epistatic interaction between *Hd2* and *Hd6*: An F_1 hybrid of NIL(*Hd2*) (Figure 4B) and NIL(*Hd6*) was developed to confirm an epistatic interaction between *Hd2* and *Hd6*. A self-pollinated population ($n = 96$) of this F_1 plant showed 27 days' variation in range in days to heading. QTL analysis showed that the segregation of both *Hd2* and *Hd6* influenced this variation (data not shown). Figure 5 shows differences among mean values of days to heading for nine genotype classes. Under field conditions, a phenotypic difference caused by the genotype of *Hd6* was observed when the genotype of *Hd2* was homozygous for Nipponbare or heterozygous, but not when the genotype of *Hd2* was homozygous for Kasalath. This result suggests that *Hd2* is epistatic to *Hd6* in the field.

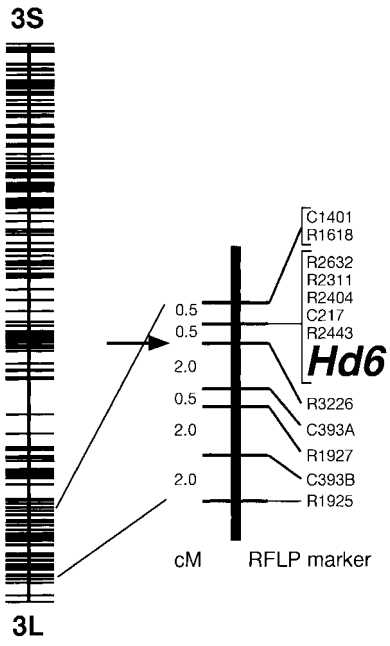

Figure 3.—Linkage map of chromosome *3*, showing the location of *Hd6*. The left vertical bar indicates an RFLP linkage map constructed from the F_2 population of Nipponbare and Kasalath (Harushima *et al.* 1998). The right vertical bar represents the linkage map constructed in this study. Map distances (cM) were calculated by the Kosambi function and are shown on the left of the bar. Names of markers and QTL are shown on the right. The arrow shows the nearest marker loci, which were estimated by Mapmaker/QTL from analysis of the BC_4F_2 population.

To further confirm the epistatic interaction between these two QTL, a day-length treatment test in a growth chamber was done with three QTL-NILs: NIL(*Hd2*), NIL(*Hd6*), and NIL(*Hd2*/*Hd6*), which is a QTL-NIL for both *Hd2* and *Hd6* (Figure 4C). Table 2 summarizes the responses of days to heading. NIL(*Hd6*) showed responses different from those of Nipponbare (explained in the previous section) and remained unheaded at 14.5-hr day length. Thus, the effect of the Kasalath allele of *Hd6*, increasing days to heading under long day length, was observed in plants homozygous for the Nipponbare allele at *Hd2* but not in those homozygous for the Kasalath allele. These results clearly support an epistatic interaction between *Hd2* and *Hd6*.

DISCUSSION

Yano *et al.* (1997) indicated that five QTL (*Hd1–Hd5*) cause variation in rice heading date in crosses between Nipponbare and Kasalath. However, they could not explain all of the variation by these five QTL, and discussed the possibilities of both imprecise estimation of gene interaction among them and failure to detect additional QTL. Our study found two additional QTL controlling rice heading date in a population derived from progeny backcrossed between the same parents (Table 1). The larger one, *Hd6*, is new; the smaller one, *Hd7*, is likely to be the same as one of three QTL reported by Lin *et al.* (1998). Judging from its estimated gene effect, *Hd6* might account for all of the previously unexplained phenotypic variation in the F_2 population described by Yano *et al.* (1997). Fine mapping revealed that *Hd6* occurs on the long arm of chromosome *3* as a single

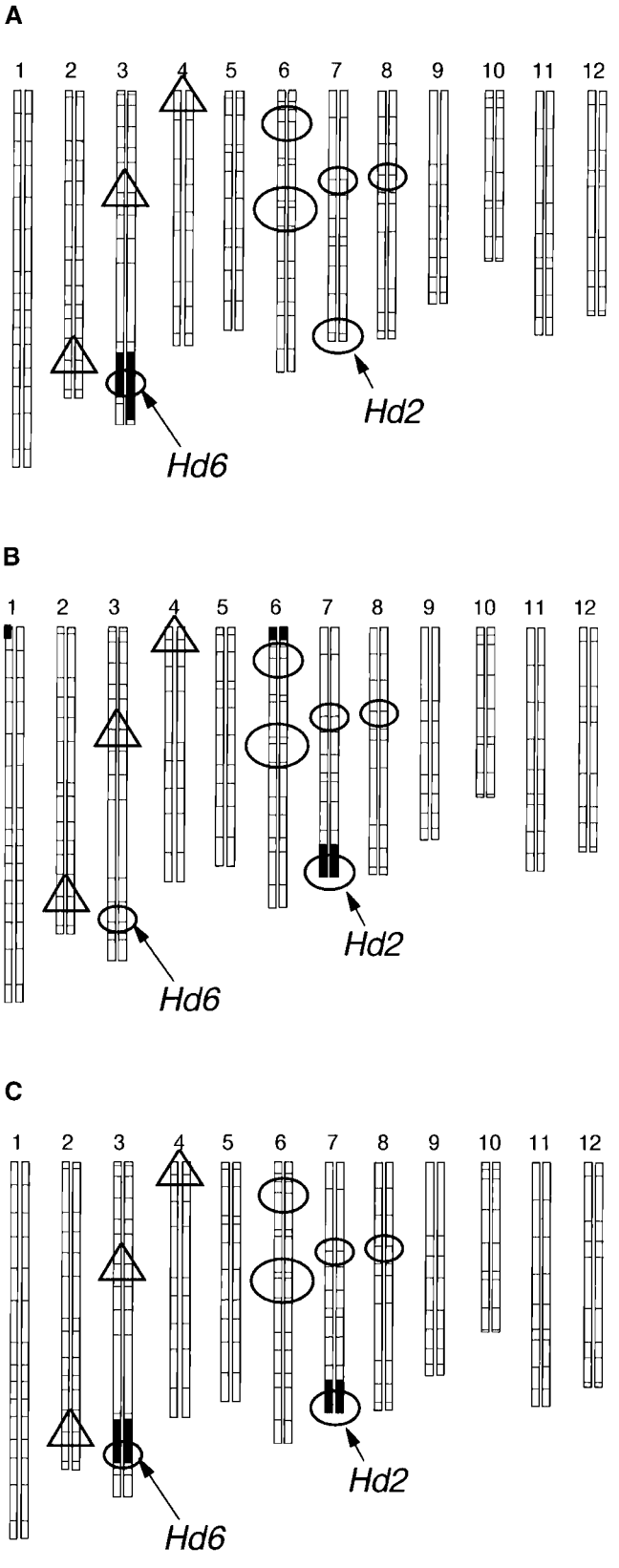

Figure 4.—Graphical genotypes of three QTL-NILs. NIL(*Hd6*) (A) and NIL(*Hd2*/*Hd6*) (C) were developed in this study. NIL(*Hd2*) (B) was developed in our group (H. X. Lin, T. Yamamoto, T. Sasaki and M. Yano, unpublished results). Ellipses and triangles are as in Figure 1.

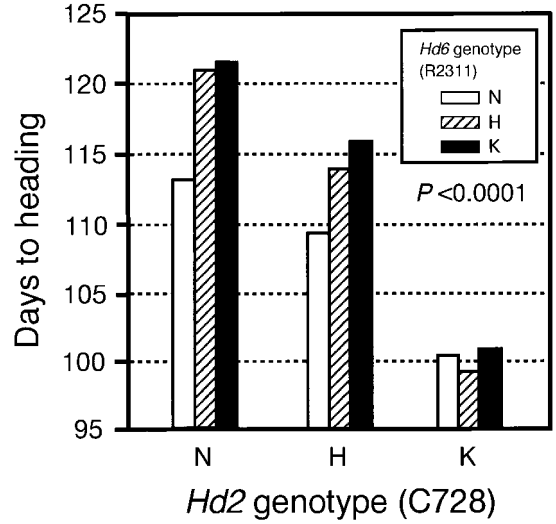

Figure 5.—Differences in mean values for days to heading in nine genotype classes of F_2 segregants derived from the cross combination between NIL(*Hd2*) and NIL(*Hd6*) under field conditions. Each genotype is represented by the two nearest marker loci (C728 for *Hd2* and R2311 for *Hd6*). N, H, and K indicate homozygosity for the Nipponbare allele, heterozygosity, and homozygosity for the Kasalath allele, respectively.

Mendelian factor (Figure 3). It will be possible to use map-based cloning to identify *Hd6*.

Relationship between *Hd6* and previously reported genes (QTL and classical mutants) controlling heading date: Some QTL on rice chromosome *3* controlling heading date have already been reported (Li *et al.* 1995; H. X. Lin *et al.* 1995; Xiao *et al.* 1995, 1996, 1998; S. Y. Lin *et al.* 1998; Xiong *et al.* 1999). Most were identified by using RFLP markers developed at Cornell University (Causse *et al.* 1994). Harushima *et al.* (1998) clarified the direction of the chromosome arms in a high-density linkage map from the Japanese Rice Genome Research Program by using RFLP markers that had been used to define the direction in the Cornell linkage map (Singh *et al.* 1996). Based on the comparison of these two linkage maps, *Hd6* might be at the same locus as both *dth3-2* and *dth3.1* reported by Xiao *et al.* (1995, 1998). To confirm this possibility, common molecular markers must be used to map both QTL. Including the major photoperiod sensitivity gene reported previously, there are now no more reported genes on the long arm of chromosome *3*.

Gene action of *Hd6*: At 13.5-hr day length in the growth chamber, the difference in days to heading between NIL(*Hd6*) and Nipponbare was ~23 days (Table 2). Based on the comparison of days to heading in three genotypes of *Hd6* when *Hd2* was homozygous for Nipponbare (photoperiod-sensitive allele), the effect of increasing days to heading was ~9 days in the field (Figure 5). These facts suggest that *Hd6* was itself the gene with strong photoperiod sensitivity, even though it had not been detected in the analysis of the F_2 population.

TABLE 2

Comparison of days to heading of three QTL-NILs and the recurrent parent, Nipponbare, under different day-length conditions

	Day length (hr)				Difference in days to heading
QTL-NIL	10.5	12.0	13.5	14.5	(14.5−10.5)
Nipponbare	44.3	49.1	75.4	>120.0	>75.7
Hd2	48.3	60.8	—	100.3	52.0
Hd6	45.3	47.4	98.7	>120.0	>74.7
Hd2, Hd6	51.7	68.3	—	104.7	53.0

All plant materials were grown in growth chambers at 28° for 12 hr and 24° for 12 hr.

Why was a QTL having a large gene effect not detected in a primary population? In the F_2 population, the LOD score of the RFLP marker near *Hd6* was 0.75 (M. Yano, unpublished data). With a score this low, it is difficult to predict the existence of a QTL; the empirical threshold level in many reports is 2.0–3.0. Although the F_2 study and this study used the same parents, Nipponbare and Kasalath, why did the results differ? Considering our day-length treatment test of some combinations of QTL-NILs, epistatic interaction might be an explanation. In the field, days to heading of the segregants homozygous for the Kasalath allele of *Hd2* were not affected by the genotype of *Hd6* (Figure 5). This suggests that *Hd6* might influence the expression of photoperiod sensitivity caused by *Hd2*. In the QTL analysis of 186 F_2 plants by Yano *et al.* (1997), the phenotypic difference caused by segregation of the chromosomal region, where *Hd6* is located, was surveyed under the situation of simultaneous segregation of two major photoperiod-sensitive QTL, *Hd1* and *Hd2*. This situation could not secure a large enough population to detect the gene effect of *Hd6*, which shows epistatic interaction. As a result, the variance due to the difference in genotypes might not be distinguishable from the variance due to the segregation of other QTL and environmental error. In summary, in QTL analysis of a population in which a QTL with a large effect will segregate, a putative gene effect of an epistatic QTL can be recognized only as a small effect, even if its actual gene effect is large. Tanksley (1993) has discussed this type of risk, where a population size is small.

The importance of evaluation of gene action by QTL-NILs: We have clearly shown that *Hd6* shows epistatic interaction with another photoperiod sensitivity gene, *Hd2* (Figure 5; Table 2). It is generally thought that epistatic interaction should be involved in quantitative inheritance. However, because ordinal QTL analyses were done with populations segregating the whole genome simultaneously, it has been difficult to detect an interaction in a specific combination of QTL genotypes. To our knowledge, some researchers have tried to detect epistatic interactions by using primary populations—such as in maize (Edwards *et al.* 1987; Stuber *et al.* 1992), tomato (De Vicente and Tanksley 1993), soybean (Lark *et al.* 1995), sorghum (Y. R. Lin *et al.* 1995), and rice (Xiao *et al.* 1995; Li *et al.* 1997; Yano *et al.* 1997; Yu *et al.* 1997)—but successful examples of detection seem to be relatively few. The more the number of contributing QTL increases, the more difficult it is to detect significant differences to distinguish individual QTL, except by using a huge population size. Yano *et al.* (1997) predicted an interaction between *Hd1* and *Hd2*, the two largest QTL. But the existence of *Hd6* and its interaction could not be detected in their analysis population (F_2). They suggested that many epistatic interactions could exist in so-called minor QTL that are not detected in the primary population.

Thus it is necessary to develop new experimental materials, such as chromosomal substitution lines or NILs, for better understanding of quantitative genetics. As in the cases of Doebley *et al.* (1995) with teosinte, Eshed and Zamir (1996) or Bernacchi and Tanksley (1997) with tomato, and this study with rice, we can understand epistatic interactions among QTL three ways: by constructing QTL-NILs for each detected QTL by MAS based on the results of primary QTL analysis, by combining QTL by crossing all QTL-NILs, and by comparing each phenotype with each combining QTL genotype. We have used this strategy and suggest that three photoperiod-sensitive QTL, *Hd1*, *Hd2*, and *Hd3*, interacted with each other. In this sense, it will be necessary to investigate epistatic interactions between *Hd6* and the other photoperiod-sensitive loci, *Hd1* and *Hd3* (H. X. Lin, T. Yamamoto, T. Sasaki and M. Yano, unpublished results).

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