

# AN UPDATED CONSENSUS MAP FOR FLOWERING TIME QTLs IN MAIZE

S. Salvi<sup>1,2,\*</sup>, S. Castelletti<sup>1,2</sup>, R. Tuberosa<sup>1</sup>

<sup>1</sup> Department of Agroenvironmental Science and Technologies, University of Bologna, Viale Fanin 44, 40127 Bologna (BO), Italy

<sup>2</sup> E. Mach Foundation - IASMA Research Centre, Via E. Mach 1, 38010 San Michele all'Adige (TN), Italy

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**ABSTRACT** - The genetic control of flowering time has been addressed by many quantitative trait locus (QTL) studies. Here, we summarise the results from 29 independent studies reporting information on 441 QTLs. The production of a QTL consensus map enabled us to identify 59 chromosome regions distributed on all chromosomes and shown to be frequently involved in the genetic control of flowering time and related traits. Additionally, the survey enabled us to empirically verify several theoretical expectations about the general outcome of QTL studies, such as mean and modal QTL number (5.1 and 3-4, respectively) per experiment, proportion of phenotypic variance explained and map resolution. The lack of molecular information about most QTLs in terms of haplotype/allele largely precludes a more complete description and understanding of the genetic architecture of flowering time in maize.

**KEY WORDS:** Flowering time; Marker-assisted selection; Meta-analysis; QTL; *Zea mays*.

## INTRODUCTION

Flowering time is a key trait directly impacting crop production as well as crop distribution, management and connected costs (DUVICK, 2005; BRUNS, 2009). In maize, early studies identified the two-week period around flowering time as the most susceptible in terms of yield loss to drought (SHAW, 1977; CAMPOS *et al.*, 2004; DUVICK, 2005). Additionally, because of its dependence from temperature, flowering time is one of the main traits potentially influenced by climate change (PORTER and SEMENOV, 2005; CRAFTURD and WHEELER, 2009).

The nature of genetic variability for flowering time in maize germplasm is mainly quantitative, with only a few mutants (*indeterminate1*, *delayed*

*flowering 1*, *Leafy* and *Early phase change*) causing a discrete phenotypic effect (NEUFFER *et al.*, 1997; COLASANTI *et al.*, 1998; VEGA *et al.*, 2002). Indeed, a range of continuous natural variation for flowering time is available in the maize germplasm, ranging from the extremely early Northern Flints shedding pollen in as few as 30 days after emergence, to the tropical varieties requiring up to four months or more to flower under long-day conditions (COLASANTI and MUSZYNSKI, 2008). The bulk of this variation was already present well before the introduction of modern breeding practices and is likely the results of the selection activity of early Native-American farmers (LABATE *et al.*, 2003). Flowering time can be rather easily modified by selection, an expected outcome given the high heritability of the trait ( $h^2 = 0.7-0.8$ ) when appropriate experimental designs are applied (HALLAUER and MIRANDA, 1981). Because of its quantitative nature, economic importance and easy scoring, the genetic basis of flowering time in maize has been extensively investigated in many QTL mapping studies.

The integration of several QTL results in single consensus maps has already been carried out for several combinations of traits and species: cyst nematode resistance in soybean (GUO *et al.*, 2006), fiber development in cotton (RONG *et al.*, 2007), yield in *Brassica* (SHI *et al.*, 2009), blast resistance (BALLINI *et al.*, 2008) and drought-related traits (KHOWAJA *et al.*, 2009) in rice, and flowering time (HANOCQ *et al.*, 2007) and head blight resistance (LIU *et al.*, 2009) in wheat. In maize, the first attempt to refer QTL studies to a common map was carried out for root architecture and other morpho-physiological traits (e.g. anthesis-silking interval) involved in the adaptive response to drought (TUBEROSA *et al.*, 2002, 2003). Subsequently, CHARDON *et al.* (2004) reviewed 22 independent maize QTL studies and obtained a consensus map with 62 flowering time QTLs spread on

\* For correspondence (e.mail: silvio.salvi@unibo.it).

all chromosomes. One of the conclusions of this work was that, despite the low number of mutants, the genetic complexity – in terms of number of genes potentially involved – of flowering in maize seems comparable to that estimated in *Arabidopsis*. Broadly confirming the results of such meta-analysis, BUCKLER *et al.* (2009) have recently reported over 50 QTLs for flowering time based on a Nested Association Mapping (NAM) approach, which represents one of the largest QTL mapping experiments so far undertaken in plants.

In maize, the number of dedicated QTL studies and the circumscribed germplasm pool make flowering time the ideal case study to (i) assess the genetic architecture of a quantitative trait, in terms of number and effects of QTLs and (ii) discuss how these data are or could be utilised in marker-assisted breeding. We also present an updated version of the flowering time consensus map originally presented in CHARDON *et al.* (2004).

## MATERIALS AND METHODS

### Collection of data

The QTL dataset was assembled by mining data already published or made available from 1992 to 2009 (Table 1), and reporting QTLs for male flowering time (days to anthesis = DTA), female flowering time (days to silking = DTS) and number of leaves (or nodes or internodes; ND) produced by the main stalk. DTA and DTS have been commonly used as indicators of flowering time in maize. ND was repeatedly shown to be highly correlated with DTA or DTS (VLADUTU *et al.*, 1999; SALVI *et al.*, 2002; LAUTER *et al.*, 2008) and characterised by high heritability (SALVI *et al.*, 2002). Hereafter, we identify as 'QTL study' a publication reporting original data with one or more sets of plants utilised for one or more QTL experiments. Only QTL studies based on genome-wide DNA-marker profiles were considered. Therefore, the results of ABLER *et al.* (1991), and LANDI *et al.* (2008) were not included because based on linkage with only a few isoenzyme or morphological markers. Additionally, we excluded QTL studies based on populations produced by crossing nearly isogenic lines (e.g. KOESTER *et al.*, 1993), since these studies would have provided (i) redundant information as to the primary QTL analyses from which were derived, and (ii) biased QTL parameters in terms of proportion of phenotypic variation explained, mapping precision, etc. Additional flowering time QTL data not reviewed here have been presented in XIAO *et al.* (2004), CHARDON *et al.* (2005), ENOKI *et al.* (2006) and BALINT-KURTI *et al.* (2006). In total, this review considered 29 QTL studies (Tab. 1).

We identify as 'QTL experiment' a QTL analysis for one trait based on a given population. Studies reporting separate QTL results for multiple environments were not considered, since they would have potentially provided redundant information which for example, would have inflated the estimates of the QTL-overview index (see below) at given map positions. Because of this, in case of multi-environment QTL studies, we recorded the data from one environment only (e.g. for well-watered and wa-

ter-stressed environments, only QTL data for well-watered conditions were considered) or alternatively, we considered the QTL results obtained on the mean values across environments, if provided by the authors. Additionally, we considered as independent QTL experiments those carried out based on different generations derived from the same initial cross, such as a QTL analysis based on a Recombinant Inbred Line (RIL) population and a QTL analysis based on the testcross progenies obtained by crossing the same RILs with a tester.

For each study and experiment, information was collected on the following: type of cross, number of progenies, trait heritability, number of QTLs, QTL position on the authors' linkage map, QTL supporting or confidence interval (SI), proportion of phenotypic variance explained (PVE) by each QTL and proportion of PVE by all QTLs. For each QTL SI, we relied on values reported in the original studies. When unavailable, SI values were estimated based on the formulas provided in DARVASI and SOLLER (1997) and GUO *et al.* (2006). We utilized the approach described by OTTO and JONES (2000) to estimate the actual number of segregating QTLs. Otto and Jones's formula estimates the total number of segregating QTLs, including the fraction which is expected to be missed, starting from an assumption on the distribution of QTL effects (e.g. exponential), the effect of the smallest detected QTL and the trait difference between parental lines.

### Flowering time consensus map

A consensus map of QTL for flowering time was assembled based on the following approach. First, each QTL from published data was projected on the IBM Genetic 2008 map ([www.maizegdb.org](http://www.maizegdb.org)). The IBM map reports thousands of markers aligned using the genetic resolution power provided by the intermated B73 × Mo17 population (LEE *et al.*, 2002), and reflects the inter-loci genetic distances using standard, single-meiosis centiMorgan (cM) units, thus facilitating the comparison of locus position and QTL confidence intervals. Projection of QTLs was carried out following the homothetic approach of CHARDON *et al.* (2004). In brief, the length of each QTL SI from the original publications was projected onto the IBM Genetic 2008 map based on the closest markers shared between the QTL study and the reference map. Each SI was therefore expanded or reduced based on rate of local expansion or reduction of the experimental map in respect to the reference map. When all QTLs were projected, we estimated the frequency (probability) of identification of a flowering time QTL for each cM position on the reference map following the approach previously described as 'QTL overview' (CHARDON *et al.*, 2004).

## RESULTS

### Number and type of studies and experiments

This survey covered 29 maize studies (Table 1) reporting QTLs for flowering time traits, including days to anthesis (DTA), days to silking (DTS) and number of plant nodes or leaves (ND). Altogether, 68 experiments were considered. As to the type of progeny, RILs (15 studies) prevailed, followed by F<sub>2:3</sub> or F<sub>2:4</sub> (10 studies), Intermated Recombinant Inbred Lines (IRILs; two studies), Introgression Library Lines (ILLs; two studies) and BC<sub>1</sub> families (one

TABLE 1 - List and main features of the studies reporting QTL results for flowering time utilised in this survey.

Parents	No. of pop.	Progeny	Size	No. of experiments	Traits	$h^2$	References
5003 × p138	1	RIL	450	2	DTA, DTS	n.a.	GUO <i>et al.</i> (2008)
B73 × B52	1	RIL	183	1	DTA	0.95	CARDINAL <i>et al.</i> (2001)
B73 × De811	1	RIL	191	1	DTA	0.89	KRAKOWSKY <i>et al.</i> (2004)
B73 × Gaspé Flint	2	ILL, BC <sub>1</sub>	75, 88	4	DTA, ND	0.89, 0.98 <sup>a</sup>	SALVI <i>et al.</i> (submitted)
B73 × H99	1	RIL	142	4	DTA	n.a.	FRASCAROLI <i>et al.</i> (2007)
B73 × H99	1	RIL	142	2	DTA, DTS	n.a.	MARINO <i>et al.</i> (2009)
B73 × Mo17	1	IRIL	298	1	DTA	n.a.	BALINT-KURTI <i>et al.</i> (2007)
B73 × Mo17	1	F <sub>2:4</sub>	112	3	DTS, DTA	n.a.	BEAVIS <i>et al.</i> (1994)
B73 × Mo17	1	IRIL	291	1	ND	0.79	LAUTER <i>et al.</i> (2008)
B73 × Mo17	1	F <sub>3</sub>	264	2	DTA	n.a.	STUBER <i>et al.</i> (1992)
B73 × Tx303	1	ILL	89	4	DTA, DTS	n.a.	SZALMA <i>et al.</i> (2007)
CML131 × CML67	1	RIL	170	2	DTS	n.a.	GROH <i>et al.</i> (1998)
CML444 × SC-Malawi	1	RIL	236	1	DTA	0.76	MESSMER <i>et al.</i> (2009)
DexF283 × F810 × F9005	6	F <sub>2:3</sub>	150	12	DTA, DTS	0.63-0.80 <sup>b</sup>	BLANC <i>et al.</i> (2003, 2006)
DO6 × D408	1	F <sub>2:3</sub>	226	1	DTA	0.85	BOHN <i>et al.</i> (2000)
ETH-DH7 × ETH-DL3	1	F <sub>2:3</sub>	226	2	DTA, DTS	0.50, 0.50	LEIPNER <i>et al.</i> (2008)
European × American	6	F <sub>2:3</sub>	100 or 200	6	DTS	n.a.	REBAI <i>et al.</i> (1997)
F2 × F252	1	RIL	129	1	DTA	n.a.	CHARDON <i>et al.</i> (2004)
F2 × F252	1	F <sub>2:3</sub>	300	1	DTS	0.91	MOREAU (2004)
F2 × Io	1	RIL	96	1	DTS	0.82	BOUCHEZ <i>et al.</i> (2002)
F2 × Io	1	RIL	100	2	DTS	0.70	MECHIN <i>et al.</i> (2001)
F2 × Io	1	RIL	86	1	DTS	n.a.	CHARDON <i>et al.</i> (2004)
Huangzao4 × CML288	1	RIL	207	2	DTA, ND	0.92, 0.90	WANG <i>et al.</i> (2008)
Mo17 × H99	1	RIL	186	2	DTA, DTS	0.88, 0.79	AUSTIN and LEE (1996)
Mo17 × H99	1	F <sub>2:3</sub>	150	2	DTA, DTS	0.82, 0.86	VELDBOOM and LEE (1996)
Mo17 × Tropical	1	F <sub>3</sub>	387	2	DTA, ND	n.a.	RAGOT <i>et al.</i> (1995)
NAM panel	25	RIL	200	2	DTA, DTS	0.83, 0.84	BUCKLER <i>et al.</i> (2009)
Tropical	1	F <sub>2:4</sub>	242	2	DTA, DTS	n.a.	REBAUT <i>et al.</i> (1996)
Z3 × 871	1	RIL	294	1	ND	0.94	Ji-HUA <i>et al.</i> (2007)

n.a., not available.

<sup>a</sup> Values referred to the ILL experiment.<sup>b</sup> Range of DTS heritability for the six F<sub>2:3</sub> populations.

study). The great majority of the studies (27) utilised single biparental crosses, while two studies were based on multiparental analyses: a diallel cross among four inbred lines (REBAI *et al.*, 1997) and a set of 25 RIL populations of the NAM study, sharing the B73 inbred as common parent (BUCKLER *et al.*, 2009). The most frequently utilised genetic background was the cross B73 × Mo17 (four studies, seven experiments), followed by B73 × H99 (two studies, six experiments), F2 × Io (three studies, four experiments) and Mo17 × H99 (two studies, four experiments). Notably, the same two RIL populations were evaluated in the experiments of BALINT-KURTI *et al.* (2007) and LAUTER *et al.* (2008), and

those of FRASCAROLI *et al.* (2007) and MARINO *et al.* (2009). The most utilised parental lines were B73 and Mo17, which were considered in ten (23 experiments) and seven (13 experiments) studies, respectively.

### Number of QTLs

The 68 experiments considered herein reported a total of 441 QTLs. By considering the 48 experiments based on biparental crosses (after excluding the ILL and NAM studies), the number of QTLs detected per experiment ranged from 0 to 17, with an average of 5.1 and a modal value of 3-4 (Fig. 1a). On average, 8.3 QTLs were reported for the six ex-

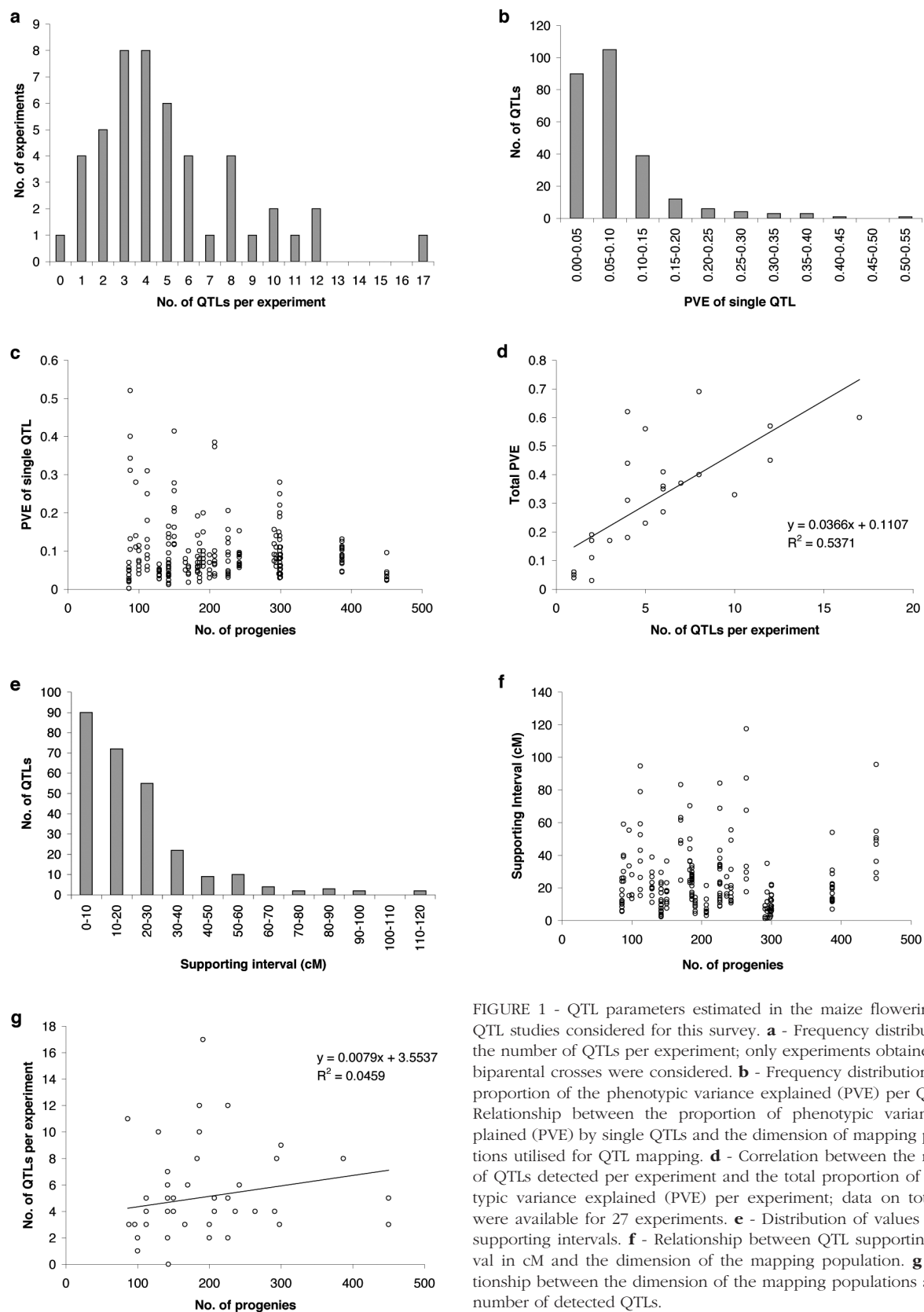


FIGURE 1 - QTL parameters estimated in the maize flowering time QTL studies considered for this survey. **a** - Frequency distribution of the number of QTLs per experiment; only experiments obtained from biparental crosses were considered. **b** - Frequency distribution of the proportion of the phenotypic variance explained (PVE) per QTL. **c** - Relationship between the proportion of phenotypic variance explained (PVE) by single QTLs and the dimension of mapping populations utilised for QTL mapping. **d** - Correlation between the number of QTLs detected per experiment and the total proportion of phenotypic variance explained (PVE) per experiment; data on total PVE were available for 27 experiments. **e** - Distribution of values of QTL supporting intervals. **f** - Relationship between QTL supporting interval in cM and the dimension of the mapping population. **g** - Relationship between the dimension of the mapping populations and the number of detected QTLs.

periments of the two ILL studies. No obvious trend linking the size of mapping populations with the number of detected QTLs was observed (Fig. 1g). By applying the OTTO and JONES (2000) approach to each experiment derived from the biparental crosses reviewed here, we estimated that ca. 53% of the total number of QTLs contributing to the phenotypic variation for flowering time was identified.

### Proportion of phenotypic variance

The distribution of PVE values for flowering time QTLs showed a typical L-shape (Fig. 1b) with most QTLs with a relatively low PVE ( $< 0.1$  for ca. 75% of QTLs). PVE values were plotted against population size (Fig. 1c). Smaller populations provided higher PVE values, indicating the presence of an upward bias in the estimates of QTL genetic effects. The proportion of variance explained by all QTLs identified in each experiment was also recorded and plotted against the number of detected QTLs (Fig. 1d): a clear trend was observed, with experiments with higher number of QTLs also characterised by higher values of total PVE ( $r = 0.73$ ,  $P 0.01$ ).

### Supporting (confidence) intervals

Considering experiments based on biparental progeny only and ignoring population size, ca. 30% of QTLs had an SI  $< 10$  cM and 90% of QTLs had an SI  $< 30$  cM (Fig. 1e). When SI values were plotted against mapping population size (Fig. 1f), no clear trend was evident.

### Genetic position of flowering time QTLs

Following the projection of 441 maize flowering time QTLs onto the reference IBM Genetic 2008 map, the QTL-overview density index was computed in order to visualize the regions most frequently involved in the genetic control of flowering time (Fig. 2). QTLs for flowering time were identified in most of the chromosome bins. The regions with the highest frequency of QTLs were bins 8.03, 8.05 and 10.04 (12, 16 and 18 QTLs, respectively). Bin 8.05 harbours the flowering time QTL *Vegetative to generative transition 1* (*Vgt1*) (VLADUTU *et al.*, 1999) which has been recently cloned by map-based cloning (SALVI *et al.*, 2007). Bin 10.04 harbours both *per se* flowering time and photoperiod-sensitive QTLs (WANG *et al.*, 2008; DUCROCQ *et al.*, 2009).

Only two chromosome segments, approximately corresponding to bins 1.09 and 9.01 were devoid of QTL SIs, and this translated in a very low QTL-overview index profile in these regions (Fig. 2). Other smaller chromosome segments devoid of QTLs were identified at telomeric regions but in these cases the lack of QTLs could also have been caused by incomplete marker coverage of the original linkage maps. We also projected on the same consensus map the position of the QTLs identified in a recent study involving the cross between B73 and Gaspé Flint, an extremely early flowering variety (SALVI *et al.*, submitted). Although B73  $\times$  Gaspé Flint was probably the widest cross in terms of both genetic distance among parents and flowering time

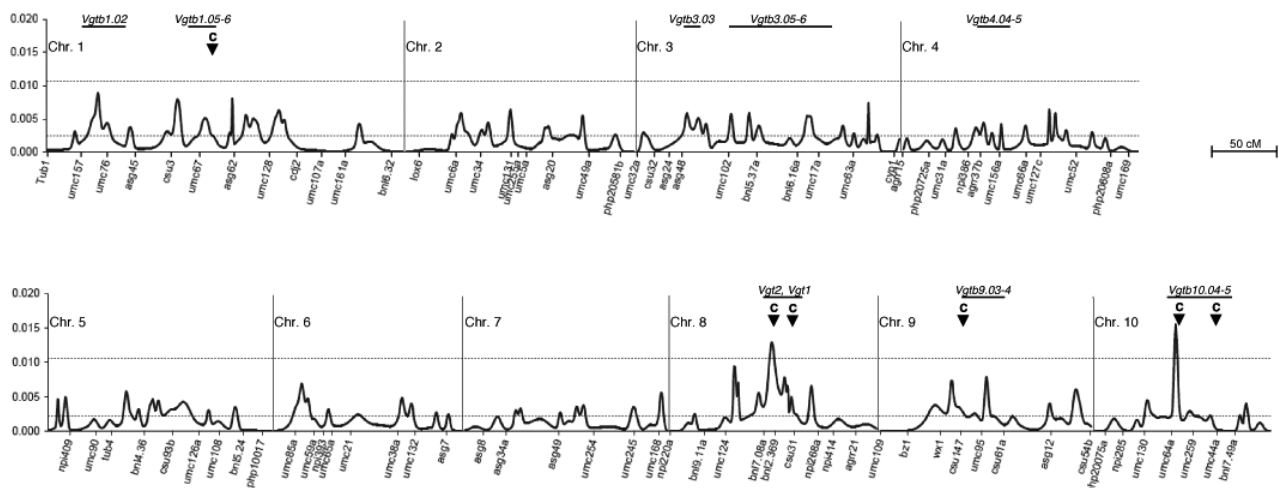


FIGURE 2 - Diagram showing the frequency of QTLs for flowering time on a reference maize linkage map. Frequency was computed as 'QTL-overview index' (CHARDON *et al.*, 2004). Data were extracted from 29 independent studies (including 68 experiments and 441 QTLs). The two dotted lines with index value of 0.00215 and 0.01075 indicate the average index and five-fold average threshold, respectively (CHARDON *et al.*, 2004). Upper label bars indicate the position of flowering time QTLs identified in a B73  $\times$  Gaspé Flint introgression library study (SALVI *et al.*, submitted). C-Black arrows indicate the position of six hot-spot QTL regions identified by CHARDON *et al.* (2004).



(ca. 30 days under U.S. Corn Belt conditions) among those surveyed here, the QTLs that were identified overlapped with those most frequently highlighted (Fig. 2). In summary, 59 regions showed a QTL-overview value higher than the average. Such regions included five of the six QTL hot spots (bins 1.06, 8.03/04, 8.05, 9.03/04, 10.04 and 10.05/06) identified by CHARDON *et al.* (2004).

#### **Level of QTL coincidence within genetic background**

In general, only a limited coincidence was observed among QTLs mapped in independent studies sharing the same biparental cross. Partial coincidence was observed between the results reported in BALINT-KURTI *et al.* (2007) and LAUTER *et al.* (2008), with two shared QTLs (at bins 8.05 and 9.07) of the three-four QTLs identified in each study, using the B73 × Mo17 IBM RILs; additionally, the Mo17 × H99 RILs tested by AUSTIN and LEE (1996) and VELDBOOM and LEE (1996) shared five QTLs out of the eight to nine QTLs reported in each study. However, two other studies sharing RILs developed from the same cross (B73 × H99; FRASCAROLI *et al.*, 2007; MARINO *et al.*, 2009) did not show any overlap.

### **DISCUSSION**

The possible applications of marker-assisted breeding (MAB) for flowering time in maize include: (i) moving tropical germplasm to temperate regions, and breeding for earliness as an escape strategy from either drought in environments with hot and dry summers or late and early frost events in short-season conditions, and (ii) breeding for increased biomass production thanks to the ontogenetic link between flowering time and leaf number and, with a lower correlation, plant height. However, reports detailing applications of MAB for flowering as well as for other traits are not common. It has been recognised that the number of reports about QTL analysis largely outnumbers (by at least a factor of three) the reports on MAB applications (BERNARDO, 2008; XU and CROUCH, 2008). Several factors are likely responsible for the existence of such QTL-MAB gap, including genetic (e.g. marker transferability across germplasm, loose marker-trait association, epistasis, QTL × environment interaction, etc.) and non-genetic factors (e.g. cost of MAB, complex logistics, access of breeding programs to QTL information, etc.; XU and CROUCH, 2008). The

marker-QTL transferability across germplasm will likely be improved when high-density genotyping coupled with the availability of QTL mapping results obtained from comprehensive QTL analyses (e.g. the NAM experiment, BUCKLER *et al.*, 2009, or association mapping studies, BELÒ *et al.*, 2008) will allow us to more accurately estimate the position and the effect of the QTLs segregating in a given breeding program.

In addition to the previous factors, the relatively high heritability of flowering time and the availability of quantitative genetic variation in all maize breeding groups have probably contributed to the limited adoption of MAB for this trait.

This notwithstanding, at least a few QTLs (for instance at bins 8.03, 8.05 and 10.04) have been repeatedly identified in multiple environments and genetic backgrounds, although genetic effects were rather variable and often small (as also indicated in the NAM experiment). Their detection in multiple genetic backgrounds and/or environments suggests that such QTL alleles could be successfully utilised in MAB under a 'breeding-by-design' framework, where allele/haplotypes at major genes/QTLs are chosen based on previously assigned breeding values and in order to pursue a specific ideotype (PELEMAN and VAN DER VOORT, 2003; SCHRAG *et al.*, 2007; SORESENSEN *et al.*, 2007). Indeed, commercially valuable inbred lines exist with the bin 8.05 Gaspé Flint haplotype (encompassing *Vgt1*) introgressed following recurrent selection for earliness (e.g. inbred lines NC264 and B73G; KOESTER *et al.*, 1993). On the other hand, the genetic architecture of flowering time (tens of loci with a few major and many minor effect genes) appears also well-suited for applying genome-wide selection, where individuals are selected based on a multimarker-estimated breeding value and disregarding any specific marker-trait association, in recurrent improvement of populations (MEUWISSEN *et al.*, 2001; BERNARDO and YU, 2007; BERNARDO, 2009). A combination of the two approaches could probably be considered when major QTLs are known to segregate together with a large number of small effect QTLs, as also suggested by BERNARDO and YU (2007).

Thanks to the increasing resolution of QTL mapping experiments, and the enhanced synteny information, particularly in cereals (BOLOT *et al.*, 2009), it is becoming increasingly possible to verify whether QTLs are shared between related species. A literature and database search showed that flowering time QTLs in rice and sorghum map at the syntenic

TABLE 2 - Comparison of rice and sorghum flowering time QTLs syntenic with the three maize chromosome bins with the highest density of flowering time QTLs. Rice and sorghum QTLs were identified using the Gramene database, based on syntenic relationships established by using CMap programme, at the Gramene website ([www.gramene.org](http://www.gramene.org)).

Maize bin	Species	Trait	Linkage group	QTL accession id <sup>1</sup>	References
8.03	Rice	Days to heading	1	AQBI001	DOI <i>et al.</i> (1998)
	Rice	Days to heading	1	AQFE003	THOMSON <i>et al.</i> (2003)
8.05	Rice	Days to heading	5	AQEA228	LI <i>et al.</i> (2003)
	Rice	Days to heading	5	AQBK013	LI <i>et al.</i> (1999)
	Rice	Photoperiod sensitivity	5	AQH024	MAHESWARAN <i>et al.</i> (2000)
	Rice	Days to heading	5	AQCU123	MEI <i>et al.</i> (2003)
	Sorghum	Days to flower	9	AQGN059	FELTUS <i>et al.</i> (2006)
	Sorghum	Days to flower	9	AQGN058	FELTUS <i>et al.</i> (2006)
	Sorghum	Days to flower	9	AQGO021	FELTUS <i>et al.</i> (2006)
10.04	Rice	Days to heading	8	AQAT005	WANG <i>et al.</i> (2002)
	Rice	Days to heading	8	AQAX019	NAKATA <i>et al.</i> (2002)

<sup>1</sup> Accession id at the Gramene database.

regions corresponding to the three most commonly reported QTLs in maize (at bins 8.03, 8.05 and 10.04; Table 2). Interestingly, among the four rice QTLs mapped at the region syntenic to *Vgt1* (bin 8.05), a typical flowering-*per se* QTL, one was photoperiod sensitive. Additionally, two flowering-*per se* QTLs that have been mapped in rice corresponded to maize bin 10.04, which harbours both photoperiod and flowering-*per se* QTLs. While additional map refinement is needed to further elucidate the correspondence of the rice and sorghum QTLs to the maize ones, it appears that the three major maize QTLs at bins 8.03, 8.05 and 10.04 do not correspond to any of the several rice QTLs that have been cloned, which were among the major ones in terms of genetic effect (YANO *et al.*, 2001; YAMAMOTO *et al.*, 2009). A formal meta-QTL analysis (VEYRIERAS *et al.*, 2007), where QTLs identified in different experiments are tested for the hypothesis to correspond to the same QTL, could probably improve the estimates of the number and the position of flowering QTLs in maize, rice, and other cereals.

Our review of published flowering time data enabled us to empirically verify several theoretical expectations and early observations about some general outcomes of QTL analysis. Based on standard biparental crosses, in each experiment an average of ca. five QTLs (ranging from 0 to 17) and a modal value of three to four QTLs were detected, both of which are close to the ca. four QTLs per experiment (range from 1 to 16) reported by KEARSEY and FARQUHAR (1998) in a review covering 176

experiment/trait combinations in different crops. A similar range of 1 to 19 QTLs was reported in a review of 52 experiments covering 222 traits across several species (LYNCH and WALSH, 1998). The application of the correction of OTTO and JONES (2000) indicates that the number of detected QTLs is a little more than half the real number of QTLs segregating for flowering time in each biparental cross. Indeed, the average number of QTLs/cross detected among the more statistically powerful NAM scheme was ca. 13 per cross (BUCKLER *et al.*, 2009). This was probably due to the high detection power provided by the 200 RILs phenotyped for each cross in an experiment characterised by high heritability and genetically highly diverse parental lines (YU *et al.*, 2008). However, in our survey, no clear relationship was observed between population size and number of detected QTLs. This was likely caused by the genetic heterogeneity of genetic materials (the number of segregating QTLs was different in the different crosses) and non-uniform map coverage among studies.

Our results highlighted an upward bias in estimating the average proportion of variance explained by each QTL (Fig. 1c) when progressively smaller populations were evaluated. Because smaller populations have inherently larger error of QTL PVE estimates, and only QTLs above a given threshold are recorded, our observations are perfectly in line with the so-called Beavis' effect (BEAVIS, 1994). A clearly L-shaped distribution of QTL effects was also observed (Fig. 1b), supporting the conclusion that flowering time, as many other quantitative traits, is

controlled by the joint action of many loci, each characterised by a small effect, and by a progressively lower number of loci with higher effect, in keeping with what was recently observed in the NAM study as well as with what observed for other traits in maize (PARISSEUX and BERNARDO, 2004) and other species (KEARSEY and FARQUHAR, 1998). The precision of QTL mapping was empirically shown to be low, with only 30% of the QTLs mapped at a resolution < 10 cM, in keeping with early predictions (DARVASI *et al.*, 1993). Additionally, both large and small populations identified QTLs with wide and narrow SI values. This is expected since population size influences both precision and power of QTL detection (DARVASI and SOLLER, 1997). Therefore, while QTLs with strong effect will be mapped with high resolution in larger populations, the increased statistical power of such populations will also permit to map additional minor QTLs at lower resolution.

The stability of QTL allelic effects across genetic backgrounds is one of the prerequisites for an effective exploitation of MAB. Indications about QTL stability can be obtained by comparing QTL experiments based on the same genetic background. Our results (based on comparison between B73 × Mo17 IBM or Mo17 × H99 experiments) indicated limited congruence, as previously observed (BEAVIS *et al.*, 1994; MIHALIEVIC *et al.*, 2004). When the comparisons involved independently developed populations that only shared the parental lines, the level of congruence was not higher than comparisons between un-related germplasms. Our and previous observations clearly imply that low statistical power of QTL analysis, different statistical approaches, heterogeneity in marker informativeness and map coverage, presence of genotype-environment interactions and genetic heterogeneity (different loci are polymorphic for different alleles in different crosses), all contribute to produce different QTL results in independent studies.

The nature and molecular structure of the genes/sequences underscoring the ca. 60 flowering time QTLs most frequently identified in the maize cultivated germplasm remain basically unknown. This notwithstanding, it is worth noting that PHILLIPS *et al.* (1993) had already theorized the positional cloning of *Vgt1*, the most important *per se* flowering time QTL, after its Mendelization, e.g. by moving the segregating locus, either coding or non-coding, in an isogenic background where the QTL would control most of the phenotypic variation for flowering time. Accordingly, *Vgt1* has now been position-

ally cloned following the approach proposed by PHILLIPS *et al.* (1993) and has been shown to correspond to an apparently non-coding, enhancer-like element mapped ca. 70 kb upstream of a gene coding for an Ap-2 like transcription factor (SALVI *et al.*, 2007). While other studies have confirmed the combination of QTL isogenization and positional cloning as a powerful approach for the molecular dissection of quantitative traits (SALVI and TUBEROSA, 2007), no other flowering time QTL has been cloned in maize using this approach, while at least five of them were cloned in rice (YAMAMOTO *et al.*, 2009). Finally, the full potential of genome-wide association mapping for gene cloning has not yet been exploited in maize because the very low linkage disequilibrium reported in this species (< 1 kb; GORE *et al.*, 2009) requires very high number of markers and limits the application of this approach to candidate-gene testing only (THORNSBERRY *et al.*, 2001; PRESSOIR *et al.*, 2009).

## CONCLUSIONS

Despite extensive QTL analyses and meta-analyses, the effective description of the genetic architecture of flowering time in maize is not yet available. Under the QTL perspective, a more complete and informative picture will only be possible when, in addition to map positions and mean genetic effects, a detailed description of the QTL haplotypes becomes available, in terms of molecular marker alleles tightly linked with the QTLs and/or of DNA sequences. Additionally, because of the very low linkage disequilibrium, in maize it is generally impossible to describe the QTL haplotypes by simply considering the markers identified as linked after mapping on standard biparental cross populations. Such description will at least require genotyping the core germplasm collections, including the founders of current germplasm, with a very large number of SNPs (in the range of several millions; GORE *et al.*, 2009) or via their full genome re-sequencing.

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