



Meta-QTL analysis and identification of candidate genes for drought tolerance in bread wheat (*Triticum aestivum* L.)

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Abstract Meta-QTL (MQTL) analysis for drought tolerance was undertaken in bread wheat to identify consensus and robust MQTLs using 340 known QTLs from 11 earlier studies; 13 MQTLs located on 6 chromosomes (1D, 3B, 5A, 6D, 7A and 7D) were identified, with maximum of 4 MQTLs on chromosome 5A. Mean confidence intervals for MQTLs were much narrower (mean, 6.01 cM; range 2.07–19.46 cM), relative to those in original QTLs (mean, 13.6 cM; range, 1.0–119.1 cM). Two MQTLs, namely MQTL4 and MQTL12, were major MQTLs with potential for use in marker-assisted breeding. As many as 228 candidate genes (CGs) were also identified using 6 of the 13 MQTLs. In-silico expression analysis of these 228 CGs allowed identification of 14 important CGs, with + 3 to – 8 fold change in expression under drought (relative to normal conditions) in a tolerant cv. named TAM107. These CGs encoded proteins belonging to the following families: NAD-dependent epimerase/dehydratase, protein kinase, NAD(P)-binding domain protein, heat shock protein 70 (Hsp70), glycosyltransferase 2-like, etc. Important MQTLs and CGs identified in the present study should prove useful for future molecular breeding and for the study of molecular basis of drought tolerance in cereals in general and wheat in particular.

Keywords Meta-QTLs · Candidate genes · Drought · Wheat

Introduction

Wheat is an important staple food crop world-wide with a history of remarkable success in improvement of productivity and production. The global bread wheat production increased steadily from 537.5 mt in 1995/96 (https://apps.fas.usda.gov/psdonline_legacy/circulars/grain-wheat.pdf) to ~ 759 mt in 2018–2019 (<https://www.uswheat.org/wheat-letter/first-look-at-2019-20-by-usda-sees-another-record-world-wheat-crop/>). It occupies 17% of crop acreage globally, feeding about 2.5 billion people (40%) in ~ 90 countries and provides 20% of total food calories and protein for human nutrition (Gupta et al. 2008). India is the third largest producer of wheat (after USA and China) in the world with an estimated production of about 106.21 mt during 2019–2020 (Economic Times, India, Jan 17 2020). According to estimates of FAO, world would require around 840 mt of wheat by 2050 (~ 24% increase over 30 years). This demand excludes the requirement of animal feed and adverse impacts of climate change on wheat production.

Drought affects 42% of global wheat area and can reduce grain yield by 58–92% (Kosina et al. 2007; Farooq et al. 2014). Therefore, drought stress continues to be an important challenge to agricultural researchers and plant breeders. It has also been estimated that drought alone causes more annual loss in crop yield than all pathogens combined together and contributes to annual global loss of \$30 billion (Gupta et al. 2020a, b). It is also estimated that by the year 2050, the demand for water will double and the supply of fresh water will reduce by 50% due to climate change

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(Gupta et al. 2020a, b). Estimates also indicate that by 2025, as many as 1.8 billion people will face absolute water shortage and 65% of the world's population will live under water-stressed environments (Nezhadahmadi et al. 2013). Thus, in order to meet the projected demand of wheat to feed the ever-increasing human population, we need to mitigate the adverse effects of drought on productivity and production of wheat. For the sustainable development of wheat varieties with high genetic yield potential that are also tolerant to drought stress, we need to identify QTLs for drought tolerance and also the candidate genes underlying the QTLs. As many as > 1200 QTLs have already been reported for different drought responsive traits in wheat (Gupta et al. 2020a, b), but the discovery of major robust QTLs with closely associated markers with a high potential for molecular breeding still remains a challenge.

Meta-QTL (MQTL) analysis has been used to identify the consensus and robust QTLs through the use of information reported in multiple studies for the reliability of their location and effect across different genetic backgrounds and environments, as well as to refine QTL positions on a consensus map (Goffinet and Gerber 2000). MQTL analysis is generally conducted using the software Biomercator V4.2, which is based on the algorithm developed by Goffinet and Gerber (2000) in which a maximum likelihood function is used to determine the following: (1) the number of MQTLs given a set of input QTLs on a common genetic map; (2) the consensus positions of detected MQTLs based on the variance in positions of input QTLs, and (3) 95% confidence interval (CI) for each MQTL based on the variance in marker intervals of input QTL (Arcade et al. 2004). More recently, whole genome sequences (pseudomolecules) have also been utilized for meta-QTL analysis (Xu et al. 2019).

MQTL analysis requires two necessary conditions, namely a consensus map with high-density markers (Hong et al. 2010; Shirasawa et al. 2013) and a large number of independent QTLs for the same trait identified from different genetic backgrounds and environments (Goffinet and Gerber 2000). Consensus QTLs obtained from meta-analysis of a number of QTLs related to a target trait at a 95% confidence interval (CI) are called MQTLs. In the past, MQTL analysis has been successfully carried out for a variety of traits in a number of crops including the following: (1) maize (Chardon et al. 2004; Wang et al. 2006; Coque et al. 2008; Truntzler et al. 2010; Hao et al. 2010; Li et al. 2011; Chen et al. 2017; Guo et al. 2018; Zhao et al. 2018), (2) rice (Ballini et al. 2008; Norton et al. 2008; Khowaja et al. 2009; Islam et al. 2019; Khahani et al. 2020), (3) cotton (Rong et al. 2007), (4) rapeseed (Shi et al. 2009), (5) potato (Danan et al. 2011), (6) cocoa (Lanaud et al. 2009), (7) soybean (Guo et al. 2006; Sun et al. 2012) and (8) apricot (Marandel et al. 2009).

MQTL analysis in wheat has also been successfully utilized to detect definitive QTL regions not only for drought tolerance (20 MQTLs for 502 independent QTLs from an earlier study; Acuña-Galindo et al. 2015), but also for several other individual traits including the following: (1) pre-harvest sprouting tolerance (Tyagi and Gupta 2012), (2) ear emergence (Hanocq et al. 2007; Griffiths et al. 2009), (3) resistance against *Fusarium* head blight (Häberle et al. 2009; Löffler et al. 2009; Liu et al. 2009), (4) plant height (Griffiths et al. 2012), (5) grain dietary fiber content (Quraishi et al. 2010), (6) seed size and seed shape (Gegas et al. 2010), (7) yield contributing traits (Zhang et al. 2010; Quraishi et al. 2017), (8) resistance to leaf rust (Soriano and Royo 2015) etc. Since large number of QTLs for drought tolerance have been reported after the last report of MQTL analysis for drought tolerance in wheat, the present study involving MQTL analysis was conducted (based on QTL studies conducted during 2015–2020) to supplement the list of MQTLs and candidate genes reported in the earlier MQTL study for drought tolerance (Acuña-Galindo et al. 2015).

Materials and methods

In the present study, meta-QTL (MQTL) analysis and identification of underlying candidate genes was undertaken utilizing the widely known five steps, which are briefly described:

Bibliographic review and collection of QTL information

A thorough bibliographic review was carried out and QTL information for drought tolerance in wheat was collected from 14 independent studies. This included information on chromosome location, most closely linked marker(s), QTL position, log of odds (LOD) value, confidence intervals (CIs) and R^2 values. Details for individual studies used in the present study are summarized in Table 1. The MQTL analysis was conducted using BioMercator v4.2 (Arcade et al. 2004).

Construction of consensus map

A consensus genetic map was developed using the following two dense composite maps: (1) a map containing 1235 SSR loci with an average distance of 2.2 cM between two adjacent markers (Somers et al. 2004) and (2) the composite map with 4506 markers available at Grain Gene 2.0 (<https://wheat.pw.usda.gov/GG3/>). All markers from the framework maps used in individual QTL studies were projected on these reference maps (applying a weighted

Table 1 Summary of QTL studies used for meta-QTL analysis during the present study

S. no.	Type of mapping population, cross, and population size	Type and number of markers	Method used for QTL analysis (no. of environments)	References
1	F ₂ , 6544-6 × Chakwal-86 (180)	SSR (425)	CIM, IM, SMA	Malik and Malik (2015)
2	RIL, W7984 × Opata M85 (105)	SSR, RFLP (1017)	CIM (2)	Onyemaobi et al. (2018)
3	DH, CO940610 × Platte (185)	SSR, DArT, STS, Protein (250)	CIM (4)	El-Feki et al. (2018)
4	RIL, W7984 × Opata85 (104)	SSR, RFLP (1475)	CIM (2)	Ayalew et al. (2018)
5	RIL, Longjian19 × Q9086 (120)	SSR (524)	CIM (4)	Yang et al. (2016)
6	DH, Excalibur × Kukri (192)	SSR, DArT (392)	CIM (22)	Gahlaut et al. (2017)
7	RIL, Langdon × G18-16 (Durum) (152)	SSR, DArT (690)	IM (2)	Peleg et al. (2009)
8	RIL, SeriM82 × Babax (194)	SSR, AFLP, DArT (587)	CIM (6)	McIntyre et al. (2010)
9	DH, Arche × Recital (222)	SSR (182)	CIM (12)	Zheng et al. (2010)
10	RIL, SeriM82 × Babax (194)	SSR, AFLP, DArT (587)	CIM (8)	Mathews et al. (2008)
11	RIL, SeriM82 × Babax (167)	SSR, AFLP, DArT (401)	CIM (3)	Pinto et al. (2010)
12	DH, Beaver × Soissons (34)	SSR, AFLP (241)	CIM (3)	Verma et al. (2004)
13	DH, RAC875 × Kukri (260)	SSR	CIM (6)	Bennett et al. (2012)
14	RIL, C306 × HUW206 (104)	SSR (141)	CIM (3)	Kumar et al. (2012)

RIL recombinant inbred line, *DH* doubled haploid, *SSR* simple sequence repeat, *DArT* diversity array technology marker, *AFLP* amplified fragment length polymorphism, *RFLP* restriction fragment length polymorphism, *CIM* composite interval mapping, *IM* interval mapping, *SMA* single marker analysis

least square method) to construct a consensus genetic map, following procedure outlined in BioMercator v4.2 (www.genoplante.org) (Arcade et al. 2004). The two maps were first integrated to provide a pre-consensus map, which was then used for developing a consensus map which carried maximum number of markers and was suitable for QTL projection to facilitate meta-QTL analysis.

QTL projection

The projection of individual QTLs on consensus map was based on their LOD score, phenotypic variation explained (PVE), confidence interval and QTL position. The software, BioMercator v4.2 (Arcade et al. 2004) was used for projection utilizing positions of markers that were common in more than one study, and following the rule that the markers flanking the interval of the original QTL should correspond to the interval on the consensus chromosome map. Therefore, finally, out of the 14 studies, information from only 11 studies was used by the software for QTL projection. The remaining three studies were dropped

by the software mainly due to missing essential information mentioned above.

Wherever the genetic position of a marker was not known, the markers closest to the flanking markers from the reference map were used to project QTL on the consensus map. The 95% confidence intervals (CIs) of original QTLs on their original maps were estimated using the following formula provided by Darvasi and Soller (1997): $CI = 530/NR^2$, where, N is the population size and R² is the proportion of the phenotypic variance explained (PVE) by individual QTL. The QTLs which could not be mapped onto the consensus map and those mapped at locations outside the consensus map were discarded.

Analysis for meta-QTL

Meta-QTL (MQTL) analysis was performed on the QTL clusters on each chromosome using BioMercator v 4.2 (Goffinet and Gerber 2000). This software allows us to find out the number (*n*) of MQTL, which is usually less than the number of total projected QTLs. This is done by selecting

one of the five models available in the software, one model for each possibility. A specific model is selected on the basis of minimum value of Akaike Information Criterion (AIC); the lower the AIC value, the more appropriate is the model. The aim of AIC is to estimate the mean log-likelihood (MELL) for the number of real positions x_i of the n QTLs (Sakamoto et al. 1986). The AIC value is computed using the following formula: $AIC = -2 \times L(\theta^{[k]}, X^{[k]}, X) + 2 \times k$, where $L(\theta^{[k]}, X^{[k]}, X)$ is the log-likelihood of the observed vector X (QTL position), k is the actual number of parameters (1, 2, 3, 4... n), and X_0 the actual value of the positions of n QTLs. K is an unbiased estimator of MELL. We have chosen the model with the minimum AIC value, as recommended.

Identification of candidate genes underlying the MQTL region and expression analysis

The candidate genes (CGs) are the genes localized within a MQTL region that is identified based on the positions of markers flanking the CI of the MQTL (or the marker closest to the flanking markers). For this purpose, nucleotide sequences of markers were retrieved from GrainGenes database (<https://wheat.pw.usda.gov/GG3>) and used for a search of genes using wheat reference genomic sequence available in EnsemblPlants database (version 082214v1, <http://plants.ensembl.org/index.html>) using BLAST (maximum E-value = $1E-100$, minimum 95% identity of the sequence). Gene models found within the physical regions corresponding to the QTL intervals were retrieved using BioMart of EnsemblPlant. In silico expression analysis for the validation of identified CGs was conducted with WheatExp database using the conserved domain sequences (CDS) of each individual candidate gene. Heat maps for expression data were prepared using ClustVis (<https://biit.cs.ut.ee/clustvis/>; Metsalu and Vilo 2015).

Results

Bibliography search for QTLs for drought tolerance

Out of 14 studies on QTL analysis for drought tolerance in wheat, listed in Table 1, in the present study only 11 studies could be used for MQTL analysis. Each study involved a separate mapping population (total 11 populations), leading to detection of as many as ~ 340 QTLs. These 340 QTLs were distributed on all the 21 chromosomes belonging to 7 homoeologous groups (1–7) and 3 sub-genomes (A, B and D). Significant differences were observed for the number of QTLs not only among all the seven homoeologous groups, but also among individual chromosomes within a homoeologous group (Fig. 1). Each

QTL is characterized by its map position [most likely position and confidence interval (CI) around this position], LOD value and the proportion of PVE (estimated through R^2 value). Whenever, the required information about position and R^2 value for the QTLs was not available from a particular study, the most likely position of QTLs was determined as the middle point between the two flanking markers, and the R^2 value of closest flanking marker was taken as the R^2 value of the QTL.

Construction of a consensus map and QTL projection

In bread wheat, a number of framework genetic maps are available, one each for an individual mapping population used for QTL interval mapping in a particular study. However, the number of common markers among the individual maps that were used in the present study were not adequate for construction of a consensus map and for the reliable projection of QTL positions. Therefore, for developing a consensus map, a pre-consensus map was first generated from two important available maps (see “Materials and methods” section for details). The pre-consensus map so developed was used for developing a consensus map using the framework maps. Following criteria were used for construction of consensus map using framework maps from 11 studies: (1) A chromosome in a framework map having no more than one common marker in the corresponding chromosome of the pre-consensus map was excluded. (2) Inversion of marker order was filtered out by discarding inconsistent loci with the exception of very closely linked markers. If two or more markers in a map are available in inverted orientation relative to pre-consensus map, then one of the two closest markers available in inverted order and separated by a distance of < 1 cM, was dropped to retain a maximum number of common markers. (3) When all the common markers were in reverse order with respect to the pre-consensus map, we used inverted genetic map for projection.

Meta-QTL analysis

Only 86 QTLs from the 340 QTLs that were identified from bibliographic search were initially selected for meta-QTL analysis, since the remaining 254 QTLs did not have common flanking markers with the markers in the consensus map. Out of these 86 QTLs, only 42 QTLs could be projected on to the consensus map based on the lowest AIC values. Out of these 42 QTLs, maximum number of QTLs was available on chromosome 5A, followed by QTLs on chromosomes 7A, 1D, 3B, 6D and 7D in that order. Remaining 44 QTLs were discarded by the software probably due to high AIC value as mentioned earlier. Using

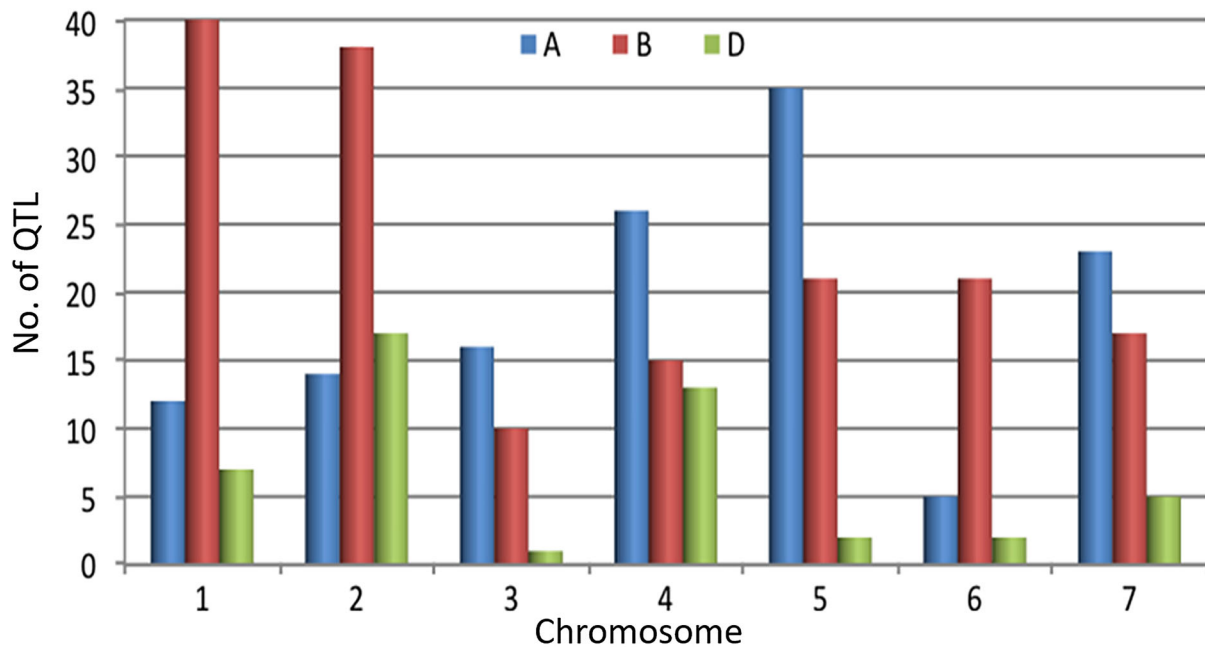


Fig. 1 Distribution of individual QTLs for drought tolerance on 7 homoeologous groups and the A, B and D sub-genomes of wheat

these 42 original QTLs, 13 MQTLs (Table 2; Fig. 2) were identified on six different chromosomes, namely 1D, 3B, 5A, 6D, 7A and 7D (for details, see Table 3). The confidence intervals (CI) for MQTLs were narrow (mean: 6.01 cM; range 2.07–19.46 cM) relative to those for the original QTLs (mean: 13.6 cM; range 1.0–119.1 cM; for details see Table 2). Further, it was observed that 10 of the 13 MQTLs, each controlled more than one trait indicating their pleiotropic nature. Out of these 13 MQTLs, following two MQTLs were important: (1) MQTL12, which is the major MQTL located on chromosome 7D with R^2 (PVE %) of 23.40%, and a confidence interval of 3.18 cM. This MQTL also had CI that was reduced by 50% (3.18 cM against original 6.10 cM). (2) MQTL4, which comprised maximum number of original QTLs (10), each controlling a separate drought responsive trait (Table 2).

Candidate genes (CGs) identified underlying the MQTLs region

In the present study, 228 drought responsive CGs were initially identified, which belonged to the following 6 MQTLs: MQTL2 (34), MQTL4 (30), MQTL5 (31), MQTL7 (20), MQTL8 (19) MQTL13 (94). No candidate genes (CGs) could be identified for the remaining 7 MQTLs, since these MQTLs were flanked by markers like AFLP/RFLP with no sequences data available for BLAST search.

Expression analysis of CGs under drought

In the database, expression data was available for only 42 of 228 CGs, and that too for a solitary drought tolerant wheat genotype TAM107. This expression data was utilized for in silico expression analysis of the CGs, and allowed us to prepare heat maps. Only 14 CGs exhibited significant changes ($FC = +3$ to -8) in expression due to drought stress (1 h and 6 h drought stress at seedling stage in tolerant cv. TAM107); for the remaining 28 CGs, although expression data was available, no significant change in expression due to drought was observed, as evident from the heat maps presented in Fig. 3. These 14 CGs showing significant changes in expression due to drought belonged to only 5 of the 6 MQTLs (Table 3); for the remaining one MQTL (MQTL7), although 20 CGs were available, but expression data was available for only three genes, and this was not sufficient for expression analysis. The 14 CGs encoded a variety of proteins and under drought stress, 11 of these CGs showed down-regulation whereas the remaining three genes showed up-regulation (for details see Table 3). These CGs can be validated through a study of their expression in seedlings of drought sensitive and drought tolerant wheat cultivars grown under moisture stress.

Table 2 Details of meta-QTLs (MQTLs) for drought tolerance identified in present study

Meta-QTL* (chromosome, genetic position in cM/physical position in Mb, CI (95%) in cM)	No. of QTLs with minimum and average CI (cM)	Mean R ² % (range of R ² %)	Markers flanking MQTL
MQTL1 (1D, 36.3/-, 7.39)	2/9.10 (9.60)	6.79 (6.47–7.12)	<i>XKsuE18a-Xhor12d</i>
MQTL2 (1D, 55.1/219.7, 6.38)	2/9.80 (9.95)	5.45 (4.90–6.00)	<i>Xcfd65-Xbarc169</i>
MQTL3 (3B, 47.9/-, 9.27)	2/4.60 (15.00)	6.35 (5.80–6.90)	<i>Xgwm685-Xgwm376</i>
MQTL4 (5A, 46.5/351.1, 3.1)	10/2.60 (14.26)	6.13 (2.58–13.00)	<i>Xwmc489-Xgwm639</i>
MQTL5 (5A, 65.2/535.1, 2.78)	5/6.68 (11.37)	8.60 (5.40–17.20)	<i>Xwmc415-Xwmc795</i>
MQTL6 (5A, 98.4/-, 2.07)	4/5.20 (11.30)	8.17 (6.32–10.50)	<i>Xcdo20-Xwmc0075</i>
MQTL7 (5A, 148.4/667.9, 2.77)	1/22.20 (22.20)	7.5 (NA)	<i>Xwmc577-Xgwm595</i>
MQTL8 (6D, 108.8/246.1, 19.46)	1/20.10 (20.10)	3.2 (NA)	<i>Xcfd1-Xcfd13</i>
MQTL9 (7A, 42.7/-, 3.86)	3/3.90 (31.96)	9.67 (7.30–13.40)	<i>XwPt-11547-Xgwm1083</i>
MQTL10 (7A, 97.4/-, 8.06)	7/13.10 (37.93)	8.90 (2.70–20.43)	<i>Xfbb186-Xbcd100</i>
MQTL11 (7A,140.3/-,2.77)	1/119.10 (119.10)	6.3 (NA)	<i>Xgwm10-XP37/M64-255</i>
MQTL12 (7D, 128.7/-, 3.18)	3/6.10 (6.100)	23.40 (4.80–38.80)	<i>Xbarc5-Xbarc154</i>
MQTL13 (7D, 149.5/139,19)	1/17.2 (17.20)	6.3 (NA)	<i>Xwmc42-Xgdm67</i>
Mean CI: 6.01	Mean of average CI 13.5	Mean R ² : 8.21	

*For each MQTL, traits for the original QTLs were as follows: *MQTL1* days to anthesis, days to maturity, *MQTL2* kernel weight, water soluble carbohydrate concentration, *MQTL3* harvest index, culm length, *MQTL4* plant height, yield, flag leaf area, flag leaf length, drought susceptibility index due to spike dry matter, days to maturity, days to anthesis, total dry matter, leaf rolling, chlorophyll content, *MQTL5* carbon isotopes discrimination, canopy temperature during grain filling, days to maturity, germination percentage, harvest index, *MQTL6* osmotic potential, days to anthesis, days to maturity, germination percentage, *MQTL7* days to heading, *MQTL8* yield, *MQTL9* total dry matter, spike dry matter, drought susceptibility index due to chlorophyll content, *MQTL10* culm length, chlorophyll content, test weight, days to anthesis, days to maturity, yield, harvest index, *MQTL11* canopy temperature during grain filling, *MQTL12* spike length, days to heading, grain filling duration, *MQTL13* leaf length, NA R² (%) values not available

Discussion

Meta-QTL analysis combines results from multiple QTL studies, permitting refinement of QTL locations and identification of closely associated molecular markers for the traits of interest. In the present study, 13 MQTLs for drought tolerance were identified in wheat. For this purpose, after thorough bibliographic search, 11 studies reporting 340 QTLs were selected. However, all the 340 QTLs could not be utilised by the software, mostly due to the following two reasons: (1) unavailability of complete information about the QTL (lack of common markers in the consensus map and those flanking the QTL) and (2) high AIC value.

A meta-QTL study for drought and heat tolerance in wheat was also conducted earlier (Acuña-Galindo et al. 2015). In this earlier study, information from 30 studies (till 2015) reporting 854 QTLs (including 502 QTLs for drought tolerance) was utilized. The present study was thus a supplement to this earlier study, and largely reports MQTLs based on QTLs reported during 2015–2020. The earlier study reported 20 MQTLs that were specific to drought stress and 43 MQTLs that were common for both heat and drought, MQTL analysis for drought tolerance have also been undertaken in other cereals like rice (Courtois et al. 2009; Khowaja et al. 2009), maize (Liu et al. 2019; Hao et al. 2010) and barley (Li et al. 2013). These MQTLs for drought tolerance reported in rice, maize and barley along with MQTL reported in two studies

(including the present study) conducted in wheat may be used in future studies to identify ortho-MQTLs and the candidate genes (CGs) for drought tolerance in cereals, as earlier done for nitrogen-use efficiency (NUE) in wheat (Quraishi et al. 2011) and for yield-related traits in rice (Khahani et al. 2020).

Drought is a complex quantitative trait involving numerous physiological processes controlled by a large number of genes, such as early flowering, plant height and osmotic adjustment (Cattivelli et al. 2008; Shabala and Pottosin 2014; Gupta et al. 2020a, b). Therefore, it is always a challenge for plant breeders to collect data on phenotype with precision and then select drought-tolerant genotypes (Hu and Xiong 2014; Tuberosa 2012). In the present study, QTLs for a fairly large number of drought responsive (> 40) traits were utilized. A critical analysis would suggest that, some individual MQTLs were based each on QTLs for only one specific trait/parameter, while others were based on QTLs for more than one traits/parameters (Table 2).

Each of the 13 MQTLs that were identified during the present study had a relatively narrow confidence interval (CI), thus providing markers that are more closely associated with the corresponding MQTL. Some of the important features of 13 MQTLs that are relevant for their use in MAS include the following: (1) *Stable MQTLs under different environments*: MQTL4 is based on 3 QTLs for days to maturity (DTM) from three different studies (Peleg et al. 2009; Pinto et al. 2010; Gahlaut et al. 2017) involving three different environments. Similarly, MQTL10 is based on two QTLs for DTM from two out of three above studies. Therefore, MQTL4 and MQTL10 were also stable for the trait DTM. (2) *More than one MQTLs for the same trait*: MQTL1, MQTL4, MQTL6 and MQTL10 were each based on QTLs for DTA and MQTL1, MQTL4, MQTL5, MQTL6 and MQTL10 were based each on QTL for DTM; see Table 2). These MQTLs, each based on more than one trait seem to be more robust. (3) *Pleiotropic MQTL*: nine out of 13 MQTLs each controlled more than one trait. For instance, MQTL4 was derived from 10 QTLs each for different traits and MQTL 10 was based on 7 original QTLs each for a different trait. Interestingly, four QTLs were common among the QTLs, on which these two MQTLs are based. Similarly, there were seven other pleiotropic QTLs (for details see Table 2). These QTLs may, therefore, each represent a complex locus, each controlling more than one drought responsive traits. The above three categories of MQTLs should prove useful not only for MAS, but also for searching CGs and possible map-based cloning.

The above 13 MQTLs were also compared with the 20 MQTLs for drought tolerance that were reported earlier by Acuña-Galindo et al. (2015). Some MQTLs identified in

the present study had markers located close to the markers flanking the MQTLs reported in this earlier study. Therefore, these markers can be considered as important for MAS. Two such MQTLs identified in the present study include MQTL2 and MQTL12; MQTL2 (chromosome 1D) was flanked by two SSR markers, *Xcfd65* and *Xbarc169*, which are respectively located at a distance of 3 cM and 2 cM from the closest markers for MQTL9 reported by Acuña-Galindo et al. (2015), so that MQTL2 of the present study may correspond to MQTL9 of this earlier study. Similarly, MQTL12 (chromosome 7D) of the present study may correspond to MQTL64 of the earlier study. Since both these MQTLs are located close to the markers *Xbarc5* and *Xbarc154*, these markers may be important for MAS, while breeding wheat cultivars for drought tolerance. Notwithstanding these two seemingly common MQTLs in two studies, 11 MQTLs identified during the present study seem to be novel, thus adding to the list of known MQTLs for drought tolerance.

The present study also supports the view that drought tolerance is affected by the cumulative effect of several QTLs for different drought responsive traits. Therefore, a breeder will have to select appropriate MQTLs for MAS to improve drought tolerance. For this purpose, a breeder may select one or more MQTLs (for drought with or without one or more other associated traits) that comprise a large number of original QTLs, each having a narrow CI. Thus, a few MQTLs out of the 13 MQTLs identified in the present study may prove to be important for the development of drought tolerant wheat varieties using MAS. We propose two of the 13 MQTLs to be relatively more important based on their specific features. These MQTL include the following: (1) MQTL12 which is the only major effect QTL with R^2/PVE % of 23.4% with a narrow CI of 3.18 cM and controlling three important traits including spike length, days to heading and grain filling duration, and (2) MQTL4 (CI = 3.1 cM and average R^2/PVE = 6.13%), which is based on 10 QTLs for 10 different drought responsive traits. These two MQTLs may be used for marker-aided introgression of independent QTLs and MQTLs in any adaptive genetic background for development of drought tolerant wheat cultivars.

CGs underlying MQTLs were also identified using wheat genomic sequences available at EnsemblPlants. Out of 228 CGs identified by us; 11 CGs were also identified in two earlier studies; three of these 11 CGs involved in drought and heat stress in wheat, encoded FAD binding domain, glycosyl hydrolase and F-box (Acuña-Galindo et al. 2015). The remaining eight CGs involving tolerance to drought stress in grasses were identified by (Swamy et al. 2011); these genes encoded proteins for ABC transporter, cytP50, zinc finger, protein kinase, glutaredoxin, F-Box, aquaporin, and NAC transcription factor.

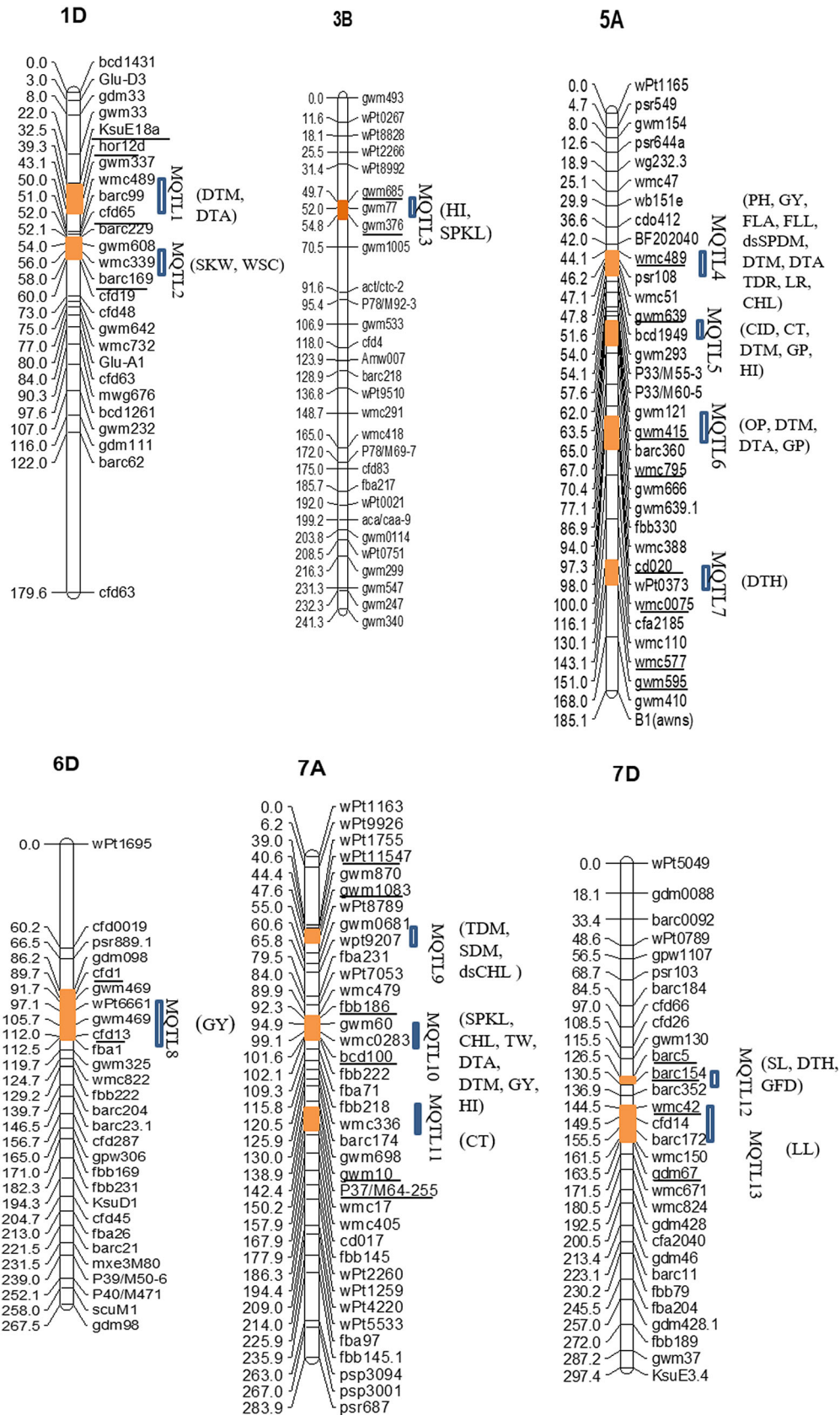


Fig. 2 Distribution and location of 13 MQTLs on 6 different chromosomes in bread wheat. The traits for the original QTLs associated with each MQTL are indicated in parenthesis against each MQTL. DTM: Days to maturity; DTA days to anthesis, DTH days to heading, HI harvest index, SPKL culm length, SKW single kernel weight, WSC water soluble carbohydrate, PH plant height, GY grain yield, FLL flag leaf length, FLA flag leaf area, dsSPDM drought susceptibility index spike dry matter, TDR total dry matter, CID carbon isotope discrimination, CT canopy temperature, OP osmotic potential, GP germination percentage, CHL chlorophyll content, LR leaf rolling, TW test weight, GFD grain filling duration, LL leaf length

Fourteen other CGs, encoding important proteins, were identified on the basis of significant change in gene expression (FC + 3 to - 8); these genes can be subjected to further studies for an understanding of the molecular mechanism of drought tolerance as well as development of markers for breeding drought tolerant wheat cultivars (for further details, see Table 3 and Fig. 3). Interestingly some of these CGs encoding NAC transcription factors, Zn finger protein, homeobox domain proteins, protein containing kinase domain and HSP70, were also earlier reported to play a role during drought stress response in cereals like rice and wheat (Min et al. 2013; Fang et al.

2014; Wu et al. 2015; Li et al. 2020). For instance, gene encoding NAC A/B superfamily protein showed down-regulation due to drought tolerance. A similar gene encoding NAC protein was earlier shown to be a potential target of a miRNA in rice where its down-regulation was shown to enhance drought tolerance (Fang et al. 2014). Similarly, downregulation of the CG encoding a kinase domain containing protein was observed in the present study. The down-regulation of a leucine-rich repeat (LRR)-RLK gene, namely LP2 (Leaf Panicle2) was also reported earlier under drought stress in rice (Wu et al. 2015); the expression of LP2 is regulated by a zinc finger transcription factor DROUGHT AND SALT TOLERANCE (DST). In contrast, genes encoding HSP70, Zn finger containing proteins and homeobox domain containing proteins showed up-regulation due to drought stress, indicating their role as positive regulators of drought tolerance. The role of Hsp70 in drought tolerance was reviewed earlier (for details, see Cho and Choi 2009). Similarly, the overexpression of wheat genes encoding a Zn finger protein (TaZnFP) and homeobox domain containing proteins in transgenic Arabidopsis showed enhanced drought tolerance (Min et al. 2013; Li et al. 2020).

Table 3 List of 14 important proteins encoded by candidate genes showing significant change in gene expression (\geq twofold or \leq -twofold)

MQTL (flanking markers/physical position in Mb)	Gene IDs (chromosome)	Predicted proteins
MQTL2 (<i>Xcfd65-Xbarc169/219.7</i>)	TraesCS1D02G156900 (1D)	NAC A/B domain superfamily \ddownarrow
	TraesCS1D02G157400 (1D)	Pyridoxal phosphate-dependent transferase, major domain \ddownarrow
	TraesCS1D02G198100 (1D)	ATPase, vacuolar ER assembly factor, Vma12 \ddownarrow
	TraesCS1D02G176600 (1D)	Zinc finger, FYVE/PHD-type \uparrow
	TraesCS1D02G207100 (1D)	Glycoside hydrolase, family 19 \ddownarrow
MQTL4 (<i>Xwmc489-Xgwm639/315.9</i>)	TraesCS5A02G038200 (5A)	Ribosomal protein L36e \ddownarrow
	TraesCS5A02G041600 (5A)	Pentatricopeptide repeat \ddownarrow
	TraesCS5A02G043400 (5A)	Homeobox domain \uparrow
MQTL5 (<i>wmc415-Xwmc795/535.1</i>)	TraesCS5A02G268800 (5A)	NAD-dependent epimerase/dehydratase \downarrow
MQTL8 (<i>Xcfd1-Xcfd13/246.1</i>)	TraesCS6D02G047800 (6D)	Protein kinase domain \downarrow
	TraesCS6D02G051300 (6D)	NAD(P)-binding domain superfamily \ddownarrow
	TraesCS6D02G049100 (6D)	Heat shock protein 70 family \ddownarrow
MQTL13 (<i>Xwmc42-Xgdm67/139.0</i>)	TraesCS7D02G190000 (7D)	Glycosyltransferase 2-like \ddownarrow
	TraesCS7D02G188500 (7D)	Peptidase M24 \uparrow

\ddownarrow = Down-regulation at 6h; \uparrow = Up-regulation at 6h; \downarrow = Down-regulation at 1h; \uparrow = Up regulation at 1h.

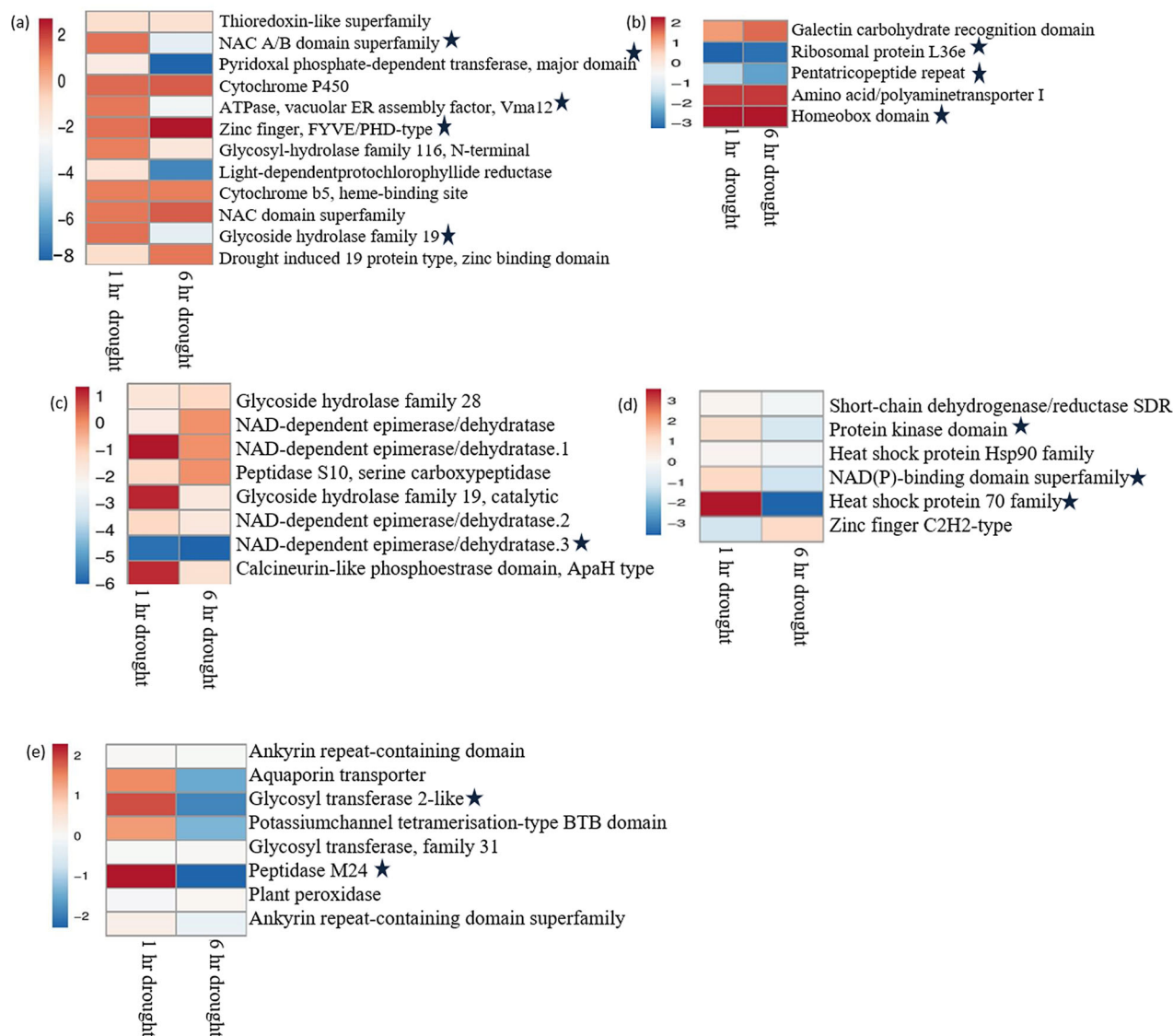


Fig. 3 Heat maps showing differential expression (in silico) of important proteins encoded by candidate genes underlying the following 5 MQTLs: **a** MQTL2, **b** MQTL4, **c** MQTL5, **d** MQTL8, **e** MQTL13. The scale shown on the left of each heatmap represents is

the fold changes ranging from +3 to –8 which differ in different heatmaps. Proteins which showed significant FC in expression are marked by an asterisk (*)

Conclusion

Thirteen key genomic regions (in the form of MQTLs) associated with agronomic performance and drought responsive traits were identified during the present study; 11 of these MQTLs were novel and two were perhaps common to those identified earlier by Acuña-Galindo et al. (2015) Two of the 13 MQTLs regions were also recommended for use in MAS for improvement of drought tolerance in wheat. Candidate genes were also identified from six of the 13 MQTL regions. These candidate genes mainly encoded proteins for ABC transporter, F box domain,

cytP50, zinc finger, protein kinase, glutaredoxin etc. Some of these proteins were also shown to be involved in drought tolerance in wheat and other cereals.

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Author contributions PKG, HSB and PKS conceived the study and also edited and finalized the manuscript. AK conducted MQTL analysis and wrote the first draft of the MS jointly with GS; JJ and KK helped AK in preparing the files for MQTL analysis.

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