Dissecting the Genetic Architecture of Leaf Rust Resistance in Wheat by QTL Meta-Analysis

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ABSTRACT

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Leaf rust is an important disease that causes significant yield losses in wheat. Many studies have reported the identification of quantitative trait loci (QTL) controlling leaf rust resistance; therefore, QTL meta-analysis has become a useful tool for identifying consensus QTL and refining QTL positions among them. In this study, QTL meta-analysis was conducted

using reported results on the number, position, and effects of QTL for leaf rust resistance in bread and durum wheat. Investigation of 14 leaf rust resistance traits from 19 studies involving 20 mapping populations and 33 different parental lines provided information for 144 unique QTL that were projected onto the Wheat Composite 2004 reference map. In total, 35 meta-QTL for leaf rust resistance traits were identified in 17 wheat chromosomes and 13 QTL remained as unique QTL. The results will facilitate further work on the cloning of QTL for pyramiding minor- and partial-effect resistance genes to develop varieties with durable resistance to leaf rust.

Leaf rust, caused by *Puccinia triticina* Erikss., is one of the major diseases of wheat (*Triticum* spp.), severely affecting susceptible cultivars and causing a large reduction in grain yield and quality worldwide (Khan et al. 2013; Kolmer 2005). Incorporating genetic resistance in the new developed varieties is the cheapest, most environmentally sustainable, and safest strategy for controlling the disease. Therefore, it is essential to identify novel resistance genes in order to protect the plants against the dynamic and rapidly evolving pathogen population (Bolton et al. 2008). To date, 72 leaf rust resistance genes, designated as *Lr*, have been cataloged (McIntosh et al. 2013) and characterized for differential reaction to single leaf rust isolates; however, they lack durability. Some of them have been mapped or assigned to wheat chromosomes (<http://www.graingenet.org>). In contrast to race-specific resistance genes, the combination of several minor or partial non-race-specific genes is the alternative for obtaining new cultivars with durable resistance. To this end, quantitative trait locus (QTL) analysis is a powerful tool for identifying and mapping both major and minor effect genes and subsequently identifying closely linked markers suitable for marker-assisted breeding.

Numerous QTL studies have been carried out in the last few years to identify genomic regions related to leaf rust resistance (Table 1). Some of the QTL colocalized with previously identified resistance genes but most of them were mapped onto other regions with small but significant effects on disease severity (DS). Synthesizing the large body of information currently available on QTL for leaf rust resistance and integrating it on a consensus map is crucial in order to speed up its exploitation in breeding programs.

Goffinet and Gerber (2000) developed QTL meta-analysis to integrate the results from independent QTL studies. The method involves the construction of a consensus map from the individual maps or, if available, the use of the organism reference map, the projection of QTL onto the consensus map, and, finally, the estimation of meta- or consensus-QTL.

The synthetic power of QTL meta-analysis is particularly useful for (i) identifying genomic regions repetitively involved in the target trait variation, (ii) narrowing down the QTL supporting intervals, and (iii) facilitating the identification of candidate genes for positional cloning. The development of specialized and user-friendly software such as BioMercator (Arcade et al. 2004; Sosnowski et al. 2012) has contributed to the widespread use of QTL meta-analysis (Salvi and Tuberosa 2015).

Some issues have to be addressed in order to perform QTL meta-analysis: (i) it requires independent QTL regarding mapping populations and environments (Goffinet and Gerber 2000); (ii) it requires information on the logarithm of odds (LOD) score, phenotypic variance explained (PVE), peak position, and supporting interval (SI) or position of flanking markers for the reported QTL; (iii) common markers must be present on the reference (or consensus) map and on the individual maps from which QTL will be projected; and (iv) the reference map must have sufficient coverage for the QTL location.

QTL meta-analyses have been performed in wheat for grain traits (Tyagi et al. 2015); plant height (Griffiths et al. 2012); sprouting tolerance and dormancy (Tyagi and Gupta 2012); dietary fiber content in grain (Quraishi et al. 2011); grain yield (Zhang et al. 2010); crop phenology (Griffiths et al. 2009; Hanocq et al. 2007); and resistance to Septoria tritici blotch (Goudemand et al. 2013), powdery mildew (Marone et al. 2013), and Fusarium head blight (Liu et al. 2009; Löffler et al. 2009; Mao et al. 2010).

The aim of this study was to identify the most important genomic regions controlling leaf rust resistance across the cultivated wheat germplasm.

MATERIALS AND METHODS

Literature collection. The literature was retrieved from the Web of Science server (<http://www.webofknowledge.com>) using the keywords “wheat leaf rust resistance QTL”. The QTL dataset was created with data available from 1999 to 2015. In total, 14 wheat leaf rust resistance-related traits, including area under the disease progress curve (AUDPC), DS, early aborted colonies, established colonies, infection efficiency (IE), infection type (IT), leaf infected area (LIA), latent period, leaf resistance (LR), lesion size, leaf tip necrosis (LTN), necrotic colonies (NEC), spore production per

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lesion, and spore production per unit of sporulating tissue (SPS), were surveyed in the current work from 19 different studies, 16 involving bread wheat (*Triticum aestivum* L.) and 3 conducted in durum wheat (*T. turgidum* L. var. *durum*).

For each study, information was collected on the following: parents of the cross, type of the cross, number of progenies, name of QTL, trait, LOD score, PVE by each QTL, QTL position on the authors' linkage map, and QTL SI. QTL meta-analysis requires independent QTL for the same trait in different mapping populations and different environments (Goffinet and Gerber 2000); therefore, when the same QTL was identified in different experiments (environments or years) in a single study, only one was considered for the meta-analysis.

QTL projection. In order to compare the QTL detected in different populations, original QTL data were projected onto the Wheat Composite 2004 map, comprising 4,403 markers, including simple-sequence repeat (SSR), restriction fragment length polymorphism, and amplified fragment length polymorphism (available at <http://www.graingenes.org>). QTL were projected following the homothetic approach proposed by Chardon et al. (2004). When the SI was reported in the study, it was used directly to establish the projected QTL peak position in the consensus map; otherwise, the distance between markers flanking the peak position of the QTL was used. When a QTL was flanked by one or two diversity arrays technology (DArT) markers, it was not possible to make a projection directly onto the Wheat Composite 2004 map due to the absence of this kind of marker on the map. In this case, markers were located first on the consensus map reported by Crossa et al. (2007), which was used as a transitional map (Hanocq et al. 2007),

and then the closest SSR marker was used for projection onto the Wheat Composite 2004 map, maintaining the map position of the original QTL (Fig. 1).

Once the QTL peak position had been projected, SI was estimated on the reference map for a confidence interval of 95%, using the empirical formula proposed by Darvasi and Soller (1997) and extended by Guo et al. (2006):

$$SI = 163 / (N \times R^2) \text{ for recombinant inbred line}$$

$$SI = 530 / (N \times R^2) \text{ for doubled-haploid progenies}$$

where N is the size of the population and R^2 the proportion of variance explained by the QTL.

The frequency (probability) of identification of a leaf rust resistance QTL for every centimorgan position of the Wheat Composite 2004 map was estimated following the approach described as "QTL-overview index" by Chardon et al. (2004). To highlight regions with noteworthy peaks, the average value of the statistic was plotted in addition to a threshold for 'high values', calculated as five times the average value of the statistic (Chardon et al. 2004).

Meta-analysis. QTL meta-analysis was conducted following the approach of Goffinet and Gerber (2000) when the number of QTL on the chromosome was 10 or less, and Veyrieras et al. (2007) when the number of QTL on the chromosome was higher than 10, using BioMercator v4.2 developed by Arcade et al. (2004) and Sosnowski et al. (2012) (available at <http://moulon.inra.fr/>). According to Goffinet and Gerber (2000), for n individual QTL, BioMercator tests the most likely assumption between 1, 2, 3, 4, and n underlying

TABLE 1. Summary of quantitative trait loci (QTL) studies included in QTL meta-analysis for leaf rust resistance in bread and durum wheat

Reference	Cross	Progeny ^a	Size	N ^b	Traits ^c	Experiments	Year	QTL (n) ^d
Azzimonti et al. 2014	Apache × Balance	DH	91	5	AUDPC, DS, IE, LP, LS, SPL, SPS	3 Environments + 2 Isolates	2009, 2010, 2011	34
Buerstmayr et al. 2014	Capo × Arina	RIL	233	8	LIA	8 Environments	2008, 2009	4
	Capo × Furor	RIL	201	4	LIA	4 Environments	2004, 2006, 2007, 2008	2
Chu et al. 2009	TA4152-60 × ND495	DH	120	1	IT, LIA	...	2007, 2008	9
Desiderio et al. 2014 ^e	MG5323 × Latino	RIL	110	2	IT, DS	2 Isolates	...	5
Faris et al. 1999	Opata85 × W-7984	RIL	114	1	IT, DS	...	...	9
Kolmer 2015	Tatcher*3 × Americano 25e	RIL	100	3	IT	3 Environments	2009, 2010	1
Lan et al. 2014	Avocet-YrA × Francolin#1	RIL	145	1	AUDPC, DS	...	2009, 2010	3
Lan et al. 2015	Avocet-YrA × Sujata	RIL	148	2	AUDPC	2 Environments	2011, 2012, 2013	5
Maccaferri et al. 2008 ^e	Colosseo × Lloyd	RIL	176	1	AUDPC, LIA	...	2006, 2007	8
Marone et al. 2009 ^e	Creso × Pedroso	RIL	123	4	DS, EA, EST, LP, NEC	4 Environments	2006, 2007	13
Messmer et al. 2000	Forno × Oberkulmer	RIL	204	4	LR, LTN	4 Environments	1995, 1996	12
Prins et al. 2011	Kariaga × Avocet	DH	250	3	AUDPC	3 Isolates	...	4
Ren et al. 2012	Bainong 64 × Jingshuang 16	DH	179	2	AUDPC, DS	2 Environments	2011	6
Rosewarne et al. 2012	Avocet × Pastor	RIL	148	1	DS	...	2000, 2002, 2004	6
Schnurbusch et al. 2004	Arina × Forno	RIL	240	7	AUDPC, LTN	7 Environments	1999, 2000	10
Singh et al. 2014	Carberry × AC Cadillac	DH	261	2	DS, LTN	2 Environments	2012	4
Tsilo et al. 2014	MN98550-5 × MN99394-1	RIL	139	3	DS	3 Environments	2005, 2009, 2010	2
William et al. 2006	Avocet × PAVon76	RIL	146	1	DS	...	1998, 1999, 2000	3
Zhou et al. 2014	SHA3/CBRD × Naxos	RIL	164	2	DS	2 Environments	2011, 2012	4

^a RIL = recombinant inbred line and DH = double haploid.

^b Number of experiments.

^c AUDPC = area under the disease progress curve, DS = disease severity, EA = early aborted colonies, EST = established colonies, IE = infection efficiency, IT = infection type, LIA = leaf infected area, LP = latent period, LR = leaf resistance, LS = lesion size, LTN = leaf tip necrosis, NEC = necrotic colonies, SPL = spore production per lesion, and SPS = spore production per unit of sporulating tissue.

^d Number of QTL.

^e Studies carried out in durum wheat.

QTL. Decision rules are based on an Akaike-type criterion, and the one with the lowest Akaike information criterion (AIC) value was considered the best fit. Following the approach developed by Veyrieras et al. (2007), meta-analysis first determines the best model based on model choice criteria of the following: AIC, AICc, AIC3, Bayesian information criterion, and average weight of evidence. The best QTL model was selected when values of the model selection criteria were the lowest in at least three of the five models. Consensus QTL from the optimum model are regarded as a meta-QTL (MQTL).

RESULTS

This survey yielded data from 19 studies carried out from 1999 to 2015 (Table 1). These studies comprised 20 different populations with 33 parental lines and a total of 3,292 progenies. Fourteen leaf rust resistance traits were considered for analysis. The traits were evaluated in a total of 52 environments over 16 years, resulting in 327 initial QTL distributed over the wheat genome.

QTL projection and analysis. The 327 QTL found were examined for fulfillment of MQTL analysis requirements (i.e., mapping populations, environments, QTL parameters, and saturation of reference map). As a result, 188 of the 327 QTL were subjected for projection onto the Wheat Composite 2004 map. Due to the insufficient common markers between the original maps and the Wheat Composite 2004 map for 44 of these QTL, they could not be projected.

The number of QTL per trait ranged from 1 for IE, NEC, and SPS to 49 for DS (Fig. 2A). In all, 32 (22%) QTL were found in genome A, 85 (59%) in genome B, and 27 (19%) in genome D. Chromosome 7B is the chromosome with the highest number of QTL (26), whereas chromosome 4A is the one with the lowest number of QTL ($n = 2$). Additionally, QTL were not detected on chromosomes 1D, 3D, 5D, and 6D (Fig. 2B).

The PVE by single QTL followed an L-shaped distribution (Fig. 2C), with the majority of the QTL showing a low PVE (<0.20 for 71% of the QTL). PVE ranged from 0.01 to 0.97, with an average of 0.20 and a median of 0.12.

The distribution between the number of QTL and size of SI ranged from 1.20 to 102.88 centimorgans (cM) (Fig. 2D), with an average of 20.79 and a median of 13.93. Approximately one-third of the QTL (35%) had an SI < 10 cM and 67% had an SI < 20 cM.

LOD scores ranged from 1.0 to 77.7, with 52% of QTL showing an LOD score of 1 to 5 (Fig. 2E). Five of the studies analyzed included as significant QTL those with an LOD score lower than 3 (Azzimonti et al. 2014; Chu et al. 2009; Faris et al. 1999; Marone et al. 2009; William et al. 2006). On the other hand, seven QTL with LOD values higher than 40.0 colocalized with previously mapped major resistance genes for leaf rust resistance (*Lr14*, *Lr19*, and *Lr68* on chromosome 7B and *Lr34* on chromosome 7D).

Overview density index. In order to visualize regions most frequently involved in the genetic control of leaf rust resistance, the QTL-overview density index (Chardon et al. 2004) was computed (Fig. 3). This statistic increases in a region with (i) the number of QTL from different experiments, (ii) the proximity between QTL positions, and (iii) the precision of the individual QTL position estimation.

The overview index was computed every centimorgan and estimates were obtained for each of the 144 projected QTL (Fig. 3). In total, 52 overview peaks were obtained, of which 47 exceeded the average value of the statistic (0.055) over the genome and represented genomic hot spots for leaf rust resistance. Of the 47 peaks, 25 showed values exceeding the high-value threshold (0.275) (Fig. 3). The number of peaks exceeding the average threshold ranged from one in chromosome 4A and 7A to five in chromosomes 1B, 2D, and 7B. For the latter, all five peaks also exceeded the high-value threshold.

QTL meta-analysis. The 144 QTL projected onto the Wheat Composite 2004 map were subjected to meta-analysis using the functions of Goffinet and Gerber (2000) when the number of QTL in a chromosome was lower than 10 and those of Veyrieras et al. (2007) when the number was 10 or more. Following an AIC, 141 QTL were grouped into 48 MQTL (Table 2). The software did not consider three QTL for meta-analysis because of their low LOD score values or large SI. In all, 35 MQTL, comprising 128 QTL, were the result

Fig. 1. Visual representation of the principle of quantitative trait loci projection from an initial map to a reference map via a transitional map, as reported by Hanocq et al. (2007) and using the homothetic approach of Chardon et al. (2004).

of the integration of at least 2 QTL, and 13 QTL remained as unique QTL (Table 2).

The number of clustered QTL ranged from 2 in 13 MQTL on several chromosomes to 11 in MQTL33 on chromosome 7B, involving seven traits and three resistance sources. The SI reported for the MQTL ranged from 0.28 to 26.17 cM (a significant reduction from the initial QTL, which ranged from 1.20 to 102.88 cM, with an average of 8.44 cM and a median of 6.73 cM [20.79 and 13.79, respectively, for the initial QTL]). This means a reduction in the SI of more than 50%.

The number of resistance traits involved in each MQTL ranged from 1 in MQTL4 and 6 to 7 in MQTL33 (Table 2).

In total, 33 of the 35 reported MQTL and all unique QTL colocalized with overview peaks (Fig. 3). Eighteen MQTL and three unique QTL coincided with peaks over the high-value threshold, suggesting that these were the most important regions involved in leaf rust resistance. Only two overview peaks on chromosomes 2D and 7B were not associated with MQTL.

Colocalization with *Lr* resistance genes. Genomic location of major *Lr* resistance genes was also analyzed in order to look for

association between major resistance genes and MQTL. To date, 72 *Lr* genes have been cataloged (McIntosh et al. 2013) and characterized for differential reaction to single leaf rust isolates, and 43 of them have been mapped or assigned to wheat chromosomes (<http://www.graingenes.org>). In all, 13 genes previously mapped on Wheat Composite 2004 were assigned directly to their map position, whereas 12 genes mapped on the Triticum Genes map and 4 genes from their original maps—*Lr22a* from Hiebert et al. (2007), *Lr68* from Herrera-Foessel et al. (2012), *Lr71* from Singh et al. (2013), and *Lr72* from Herrera-Foessel et al. (2014)—were projected onto the Wheat Composite 2004 map following the homothetic approach of Chardon et al. (2004).

The position of previously mapped *Lr* genes in relation to MQTL and overview peaks was included in Figure 3. Genes mapped on chromosomes 1D (*Lr21*, 0.0 cM and *Lr60*, 0.0 cM), 3D (*Lr24*, 115 cM), and 5D (*Lr1*, 100 cM) are not shown on the map because no QTL for these chromosomes have been projected. Seven *Lr* genes colocalize with five MQTL on chromosomes 1A (MQTL1-*Lr10*), 1B (MQTL5-*Lr46*), 2B (MQTL8-*Lr13*-*Lr23*), 4D (MQTL20-*Lr67*), and 7B (MQTL33-*Lr14*-*Lr19*). All of these MQTL except

Fig. 2. Parameters estimated in quantitative trait loci (QTL) studies collected for the meta-analysis; cM = centimorgans. Frequency distribution of the number of QTL by **A**, trait; **B**, chromosome; **C**, phenotypic variance explained (PVE); **D**, supporting interval; and **E**, logarithm of odds (LOD) score.

MQTL1 correspond to peaks over the high-value threshold for the overview index. Tight associations were found for *Lr71* with MQTL2 on chromosome 1B, *Lr27* with MQTL15 on chromosome 3B, *Lr68* with MQTL33 on chromosome 7B, and *Lr34* with MQTL34 on chromosome 7D. MQTL34 included two overview peaks and the resistance gene colocalizing with one of them, although it is outside the MQTL SI (Fig. 3). The rest of the *Lr* genes were mapped at positions without MQTL. *Lr39* and *Lr72* were positioned in regions with overview peaks. *Lr39* on chromosome 2D slightly exceeded the average overview value.

DISCUSSION

Since ancient times, leaf rust has been known to cause major production losses in wheat (Khan et al. 2013; Kolmer 2005). The release of cultivars with durable resistance is a major target for wheat breeding programs. To date, 72 designated genes for resistance to leaf rust disease (*Lr*) have been cataloged (McIntosh et al. 2013) and characterized for differential reaction to single leaf rust isolates. These race-specific resistance genes are easily overcome by the pathogen population but a combination of three to four slow-rusting genes with minor to intermediate but additive effects leads to resistance durability (Desiderio et al. 2014; Singh et al. 2001).

The ability to transfer target genomic regions associated with leaf rust resistance in wheat using molecular markers has resulted, in the past few years, in extensive QTL mapping experiments involving a number of populations and testing environments. MQTL analysis may help to remove redundancies and allow the more robust and reliable QTL to be identified (Goffinet and Gerber 2000).

QTL meta-analysis helps to integrate the QTL information available in order to determine regions of the genome that are

repetitively involved in trait variation and to narrow down the SI of QTL. The results of QTL meta-analysis are strongly dependent on the precision of the initial QTL mapping, SI, and projection quality (Goffinet and Gerber 2000). In the current study, we only used QTL fulfilling the requirements for QTL projection following the homothetic approach of Chardon et al. (2004) and the BioMercator v4.2 software. QTL data from 19 independent studies comprising 20 different mapping populations were collected. After a preliminary examination of the QTL information reported by the authors, 144 QTL were projected onto the Wheat Composite 2004 map (<http://www.graingenes.org>). All QTL were projected following the homothetic approach of Chardon et al. (2004). To project DArT markers onto the Wheat Composite 2004 map, we used the map reported by Crossa et al. (2007) as a transitional map (Hanocq et al. 2007) for searching tightly linked SSR markers.

The low PVE values for most of the single QTL supports the conclusion that the traits reported are controlled by the joint action of many loci, each one characterized by a small effect.

The highest effects were found in QTL located on chromosome 7B in a region where three major resistance genes were mapped (*Lr14*, *Lr19*, and *Lr68*) (Fig. 3). The analysis also showed that the precision of single QTL mapping was low, with only 35% of the QTL having an SI lower than 10 cM.

QTL meta-analysis. QTL meta-analysis performed in this work revealed the presence of 48 genomic regions involved in leaf rust resistance. Of these, 35 were consensus QTL carrying at least two initial QTL (named MQTL) and 13 QTL remaining as unique QTL. The usefulness of QTL projection in highly saturated linkage maps and meta-analysis reside in defining and refining the QTL positions. Considering only MQTL, the number of QTL on the wheat genome was reduced by 73%, narrowing down their SI to

Fig. 3. Overview and meta-analysis of quantitative trait loci (QTL) affecting leaf rust resistance in wheat. The overview statistic was calculated every 1 centimorgan (cM) and plotted along each chromosome (blue curve). Two horizontal dashed lines are the average value of the statistic (0.055) and the threshold for high values (0.275), defined as five times the average value (Chardon et al. 2004). Bars below the overview curve represent the wheat chromosomes where QTL have been projected. Light gray (green) boxes represent meta-QTL harboring at least 2 QTL, whereas dark gray (red) boxes represent unique QTL. Positions of previously mapped *Lr* genes in wheat are represented by triangles below chromosome bars; *Lr* genes colocalized with meta-QTL are indicated in darker gray (blue).

50% and increasing the mapping precision. Additionally, when initial QTL showed low values for LOD score, meta-analysis helped in verifying whether those QTL belong to significant genomic regions (supported by meta-analysis and overview index). Robust SSR markers flanking MQTL were also identified and can be compared and transferred in future studies.

QTL data compilation showed that all wheat homologous groups of chromosomes are involved in the genetic control of leaf rust resistance, with only chromosomes 1D, 3D, 5D, and 6D lacking (projected) QTL. Chromosomes 3D and 5D showed initial QTL that could not be projected due to the absence of common markers with the Wheat Composite 2004 map. However, no QTL were found on 1D and 6D in the 19 studies used for meta-analysis.

The highest number of MQTL, including unique QTL, was shown by genome B ($n = 23$), followed by genome A ($n = 15$) and genome D ($n = 10$). The low variation of genome D has been recently supported by the results of a bread wheat study that located only 10.8% of the markers on it (Li et al. 2015). In agreement with the results of the current study, genome B harbored the highest number of markers (56.3%) and QTL (55.5%) (Li et al. 2015). These results support those reported by Wang et al. (2014) using a 90K SNP (single nucleotide polymorphism) array to characterize the genetic diversity of bread wheat.

The value of meta-analysis was supported by the QTL-overview density index (Chardon et al. 2004), computed in order to visualize regions most frequently involved in the genetic control of leaf rust

TABLE 2. Summary of meta-quantitative trait loci (MQTL) information for leaf rust resistance^a

Chromosome	MQTL	Position (cM)	SI (95%)	Flanking markers	QTL (n) ^b	Trait ^c	Resistance source
1A	MQTL1	27.64	11.73	Xfba254–Xwmc95b	4	AUDPC, DS	Apache, Sujata
1B	MQTL2	55.57	1.86	Xcdo98.2–Xmwg837b	6	AUDPC, DS, IT, LTN	Forno, MG5323, Oberkulmer, Pastor, Sujata
	MQTL3	88.50	8.46	Xbarc81–Xfba294	2	AUDPC, DS	Bainong 64
	MQTL4	110.39	2.10	Xfba266c–Xksu127	2	DS	Pastor, Pavon 76
	MQTL5	113.52	0.28	Xksu127–Xbarc80	2	AUDPC, DS	Francolin#1
2A	MQTL6	69.11	4.62	Xglk554–Xcmwg682b	2	AUDPC	Colosseo, Forno
2B	MQTL7	58.12	3.68	Xgwm55–Xgwm429	4	AUDPC, DS, IT	Carberry, Kariaga, Avocet S, W-7984
	MQTL8	86.05	12.44	Xwmc265–Xgwm877.1	7	AUDPC, DS, LP	Apache, Creso
2D	MQTL9	30.10	9.32	Xgwm455–Xbcd718	3	AUDPC, DS	Balance, Forno, MN99394-1
	MQTL10	56.42	8.40	Xfba74a–Xgwm30.1	3	AUDPC, DS, LTN	Forno, Pastor
	MQTL11	93.17	4.11	Xcdo1008–Xksud23a	6	AUDPC, DS, SPS	Balance
3A	MQTL12	68.25	6.73	Xcdo1345–Xgwm2	2	LR, LTN	Forno, Oberkulmer
	MQTL13	112.58	21.45	Xcfa2134–XgbxG242	2	IT, LIA	TA4152-60
	MQTL14	130.93	2.32	Xmwg570–Xcdo113	2	AUDPC, LIA	Lloyd
3B	MQTL15	12.34	2.08	XksuG30a–Xgwm533a	9	DS, IE, IT, LIA, LP, SPL	Balance, Capo, Opatá 85
	MQTL16	49.26	0.89	Xgwm566–Xgwm888.3	3	DS, IT, LIA	Francolin#1, TA4152-60
4A	MQTL17	54.67	11.17	XgbxR247–Xpsr593.2	2	DS, IT	Opatá 85
4B	MQTL18	19.22	11.80	Xgwm495a–Xcsu25	3	AUDPC, DS	Avocet S, Creso, Forno
	MQTL19	60.69	13.65	Xgwm131.2–Xmwg11a	2	DS, LTN	Carberry, Oberkulmer
4D	MQTL20	66.18	2.50	Xbarc98–Xfbb336	3	AUDPC, IT, LIA	Sujata, TA4252-60
	MQTL21	93.01	21.15	Xcdo1312a–Xfba177b	4	AUDPC, DS, LS, SPL	Balance
5B	MQTL22	47.66	4.79	Xbarc4–Xgwm371	2	AUDPC, DS	Kariaga, SHA3/CBRD
	MQTL23	140.81	8.83	Xpsp3065–Xgwm118	5	IT, LIA, LTN	Americano 25e, Capo, Carberry, TA4152-60
6A	MQTL24	39.98	16.89	Xmwg67.1–XksuH4.2	6	AUDPC, DS, LP	Balance
6B	MQTL25	51.50	19.91	S25M19_7–Xcdo476.2	2	AUDPC, DS	Bainong 64
	MQTL26	92.00	24.59	Gpc-B1–Xwmc388a	2	AUDPC, DS	Bainong 65
	MQTL27	134.25	26.17	Xgwm133b–Xfbb130	2	DS, IT	Pavon 76, TA4152-60
	MQTL28	158.00	6.91	Xbarc134–Xwmc417b	2	AUDPC, DS	Kariaga, Pastor
7A	MQTL29	77.00	4.73	XWC2028g–P78/M49.4	5	AUDPC, DS	Balance
7B	MQTL30	30.06	3.58	Xwmc335–Xgwm68.2	5	AUDPC, DS, LIA	Colosseo, Forno, Kariaga, SHA3/CBRD
	MQTL31	62.59	2.17	S25M15_19–Xgwm112	4	DS, IT, LTN	MG5323, Oberkulmer
	MQTL32	91.92	4.42	Xwmc273c–Xwmc311	4	AUDPC, DS, LTN	Forno, Oberkulmer, Opatá 85, Pastor
	MQTL33	105.53	0.53	Xgwm577–Xbarc340.2	11	AUDPC, DS, EA, EST, LIA, LP, NEC	Colosseo, Creso, Sujata
7D	MQTL34	73.73	1.75	Xbcd1438–Xcnl6b	3	AUDPC, DS, LTN	Forno, MN98550-5
	MQTL35	110.00	9.39	Xgwm44–Xcfa2174c	2	DS, LTN	Oberkulmer, Opatá 85
1A	...	123.5	12.42	Xwmc237–XksuE11.1a	1	DS	SHA3/CBRD
1B	...	36.68	6.13	XksuF43.1–Xabc155c	1	LIA	Capo
2A	...	44.00	22.09	Xfbb329–Xgwm339	1	LP	Creso
	...	63.28	3.09	Xfbb353.2–Xglk554	1	LIA	Colosseo
2B	...	70.15	4.98	Xwmc344–XksuD22	1	LIA	Capo
	...	113.60	4.27	Xfba310.1–Xbcd1231	1	LIA	Capo
2D	...	75.56	16.65	Xwmc243–Xgwm608.3	1	DS	SHA3/CBRD
5A	...	2.00	5.55	Xcnl6b–Xgwm154a	1	LTN	Oberkulmer
	...	47.50	18.38	Xbcd508–Xfbb255x	1	DS	Pastor
	...	102.99	13.26	Xwg114a–P43/M62-5	1	EA	Creso
6A	...	156.33	9.88	Sr26–P38/M51-4	1	LTN	Oberkulmer
7D	...	59.00	3.48	XgbxG564–Yr18	1	DS	Opatá 85
	...	190.08	33.85	Xgwm121–Xbarc53	1	LTN	Carberry

^a The upper part of the table shows MQTL comprising at least two clustered QTL and the lower part shows QTL remaining as unique QTL.

^b Number of QTL.

^c AUDPC = area under the disease progress curve, DS = disease severity, EA = early aborted colonies, EST = established colonies, IE = infection efficiency, IT = infection type, LIA = leaf infected area, LP = latent period, LR = leaf resistance, LS = lesion size, LTN = leaf tip necrosis, NEC = necrotic colonies, SPL = spore production per lesion, and SPS = spore production per unit of sporulating tissue.

resistance. In all, 57% of the MQTL colocalized with overview peaks above the high-value threshold, indicating them as the most reliable and robust consensus QTL.

Colocalization of resistance traits. Most of the MQTL clustered QTL representing two or more different resistance traits. This result could indicate a tight linkage of different genes, the action of genes with pleiotropic effects, or a bias due to the use of related traits measuring the same resistant component by different means. Although the potential action of tightly linked genes cannot be rejected, the hypothesis of a pleiotropic effect of a leaf rust resistance QTL was postulated by Messmer et al. (2000) for QTL controlling adult plant LR and LTN because, in their experiments, half of the QTL for LR coincided with QTL for LTN. The hypothesis of Messmer et al. (2000) was later confirmed by Schnurbusch et al. (2004), who also found a high phenotypic correlation between LR and LTN. Using two rust isolates, Desiderio et al. (2014) found significant correlation coefficients between IT and DS, suggesting that both traits might be under a common genetic control. This hypothesis was further confirmed by the overlapping LOD score curves found for the major QTL on the short arm of chromosome 1B. On the other hand, Azzimonti et al. (2014) concluded that different genetic factors are involved in the expression of leaf rust resistance components in bread wheat. However, when they are related, they may share the same QTL region; the involvement of genes with pleiotropic effects is ruled out.

Breeding implications. Excluding MQTL showing linkage with known major or race-specific *Lr* genes, some genomic regions appear as candidates to harbor new sources of resistance. According to Löffler et al. (2009), three criteria must be taken into consideration when selecting MQTL for use in breeding: they should have a small SI, a high number of initial QTL clustered, and a high effect corresponding to high PVE by initial QTL. Following these criteria, with the support of the overview index, five MQTL were found in the current study to meet these requirements: MQTL7, MQTL14, MQTL29, MQTL30, and MQTL31.

MQTL7 was located on chromosome 2B, clustering four QTL from three different traits and four sources of resistance, and comprising a genetic interval of 3.68 cM. For this cluster, Faris et al. (1999) found that the peroxidase locus (*Per2-2B*), which was mapped close to *Lr23*, was associated with resistance to the isolates used in the experiment and explained 33.1% of phenotypic variation for IT and 15.7% for DS. However, the low mapping resolution of this study did not allow determination of whether the significance of *Per2-2B* was due to the presence of the peroxidase itself or whether the effects were due to the linkage with *Lr23*. Prins et al. (2011) found a QTL between markers wPt5556 and wPt6278 covering a region of 13 cM and explaining 19.9% of the phenotypic variance. The authors postulated that, based on the genetic constitution of the mapping population parents, it was most likely that *Lr13* (present in 'Avocet S') provided resistance to two of the isolates used in the experiments. However, although located in chromosome 2B, *Lr13* is associated with the marker wPt3132 mapped outside the QTL region described by Prins et al. (2011).

Singh et al. (2014) found that the QTL *QLr.spa-4B*, located on chromosome 4B, was epistatic with LR loci on chromosomes 2B and 3B and acted not only as a main effect QTL but also as a modifier locus.

MQTL14 was located on 3A, with an SI of 2.32 cM and carrying two QTL from two traits, AUDPC and LIA, and one resistance source, durum wheat 'Lloyd'. Although Lloyd showed a susceptible phenotype across the field experiments carried out by Maccaferri et al. (2008), both QTL had a significant effect (19.1 and 30% of the PVE for AUDPC and LIA, respectively) that was detectable only in early to medium stages of the disease.

MQTL29 on 7A, with an SI of 4.73 cM, clustered five initial QTL from two different traits and one resistance source. All the QTL reported in this cluster were detected by Azzimonti et al. (2014) in

'Balance' wheat, with effects ranging from 29 to 69% of PVE, and were not isolate specific.

MQTL30 (SI 3.58 cM) clustered five QTL from four independent studies. Maccaferri et al. (2008) identified two QTL carried by 'Colosseo' conferring partial resistance to leaf rust that could play an important role in durable resistance, as postulated by Martínez and Rubiales (2002) for 'Creso', one of the parents of Colosseo. The other minor-effect QTL clustered in MQTL30 were identified for AUDPC by Schnurbusch et al. (2004), with a PVE of 8.8%, and by Prins et al. (2011), with a PVE of 2.5%; and for DS by Zhou et al. (2014) in a common position with Schnurbusch et al. (2004).

MQTL31 on 7B (SI 2.17 cM) clustered four QTL. Messmer et al. (2000) detected a minor QTL for LTN across three environments showing epistatic effects with other QTL on 3A and 7B. Desiderio et al. (2014) found a significant region on chromosome 7B associated with IT for three rust isolates and with DS for one isolate. In this region, these authors detected sequences coding for a fascilin-like protein, FLA14, and a cellular nucleic-acid-binding protein. Additionally, syntenic regions were detected with chromosomes 1, 6, and 10 of *Brachypodium distachyon*, *Oriza sativa*, and *Sorghum bicolor*, respectively, containing genes coding for protein kinases, ligases, transcription factors, and several leucine-rich repeat receptor-like kinases.

Other major QTL without linkage to known *Lr* genes have been found within the studies used to collect QTL information. On chromosome 1B, Desiderio et al. (2014) detected a major resistance gene from 'MG5323' with a PVE ranging from 41.37 to 49.51%, depending on the analyzed trait, and William et al. (2006) reported a major QTL from 'Pavon 76'. These QTL were clustered in MQTL2 and MQTL4, respectively. On the long arm of chromosome 7B, Maccaferri et al. (2008) found a major QTL (*QLr.ubo-7B.2*) for leaf rust resistance controlling both seedling and adult plant resistance, with the favorable allele inherited from Colosseo. This QTL showed a PVE for AUDPC of 72.9% and was mapped in a gene-dense region carrying several genes per QTL for resistance to rusts and other fungal pathogens. In the same region, Marone et al. (2009) identified a major gene from Creso involved in determining hypersensitive response and partial resistance. Both QTL clustered in MQTL33, suggesting that they correspond to the same locus based on the origin of Colosseo.

The use of the resistant sources carrying these QTL may help to achieve durable resistance in the breeding programs. The use of MQTL-linked markers will allow the development of marker-assisted breeding for the introgression of the selected QTL. Given the low PVE by minor or partial resistance genes, after selection of genotypes by molecular markers, an accurate phenotypic selection must complete the breeding process.

Conclusions. The current study aimed to locate consensus QTL for leaf rust resistance in wheat. After meta-analysis, 91% of the QTL clustered in consensus QTL regions over the genome and 9% remained as unique QTL. Meta-analysis allowed us to reduce the SI of the resulting MQTL in comparison with those reported for the initial QTL, thus facilitating the search for candidate resistance genes in the available databases. This study allowed us to identify genuine and stable MQTL and the associated molecular markers that can be used for marker-assisted selection for leaf rust resistance. Breeders may use this information for selecting resistant parents with QTL on different chromosomes or appropriate MQTL together with the right allelic composition of linked molecular markers, leading to a successful application of marker-assisted breeding.

QTL meta-analysis has been suggested as one of the most important approaches to help interpret the plethora of QTL information available from different studies. However, the current meta-analysis still lacks the integration of QTL haplotype information and there is no protocol for integrating QTL results from experimental populations with those from genome-wide association studies.

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