Quantitative Trait Loci Conferring Leaf Rust Resistance in Hexaploid Wheat

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Accepted for publication 6 September 2018.

ABSTRACT

Leaf rust, caused by the fungal pathogen *Puccinia triticina*, is a major threat to wheat production in many wheat-growing regions of the world. The introduction of leaf rust resistance genes into elite wheat germplasm is the preferred method of disease control, being environmentally friendly and crucial to sustained wheat production. Consequently, there is considerable value in identifying and characterizing new sources of leaf rust resistance. While many major, qualitative leaf rust resistance genes have been identified in wheat, a growing number of valuable sources of quantitative resistance have been reported. Here we review the progress made in the genetic identification of quantitative trait loci (QTL) for leaf rust resistance detected primarily in field analyses, i.e., adult plant resistance. Over the past 50 years, leaf rust resistance loci have been assigned to genomic locations through chromosome analyses and genetic mapping in biparental mapping populations, studies that represent 79 different wheat leaf rust resistance donor lines. In addition, seven association mapping studies have identified adult plant and seedling leaf rust resistance marker trait associations in over 4,000 wheat genotypes. Adult plant leaf rust resistance QTL have been found on all 21 chromosomes of hexaploid wheat, with the B genome carrying the greatest number of QTL. The group 2 chromosomes are also particularly rich in leaf rust resistance QTL. The A genome has the lowest number of QTL for leaf rust resistance.

THE HOST–RUST SYSTEM

Hexaploid wheat (*Triticum aestivum* L.; AABBDD) is believed to have originated some 10,000 years ago (Tanno and Willcox 2006) from one, or more, rare independent hybridization events between tetraploid emmer wheat (*Triticum dicoccoides*; $2n = 4x = 28$, AABB) and the diploid grass *Aegilops tauschii* ($2n = 2x = 14$, DD) (Nesbitt and Samuel 1996). Wheat provides one-fifth of the calorie intake of the world's human population and is therefore a major contributor to global food security (Food and Agriculture (FAO) 2015). However, fungal diseases are a significant factor impacting cereal production, and for wheat the three rusts; leaf

(brown), stripe (yellow), and stem (black) rust, caused by *Puccinia triticina*, *P. striiformis* f. sp. *tritici*, and *P. graminis* f. sp. *tritici*, respectively, are major global problems.

References to wheat rust are found in the Old Testament of the Bible and in ancient Roman text, indicating historically the extent to which these diseases have been a problem for cereal production (Chester 1943; Levine 1919). While stem and stripe rust are considered more damaging than leaf rust, leaf rust (Fig. 1) is more persistent and widespread, making it a significant problem year-on-year (Huerta-Espino et al. 2011). Yield losses in wheat from *P. triticina* infections are usually the result of decreased numbers of seeds per spike and lower seed weight (Huerta-Espino et al. 2011). Currently, fungicides are widely used to control wheat rusts. However, in many countries limited access to appropriate fungicides and inappropriate application can seriously affect the efficacy of the fungicide, while also having negative consequences on human health and the environment and increasing production costs (Kumar et al. 2013). Consequently, the introduction of effective and potentially durable genetic resistance into new wheat varieties is the preferred approach to rust control, providing a more effective, economic and environmentally friendly approach (Singh et al. 2000). A glossary of the terms used in this review to describe the phenotypic differences between rust resistance loci can be found in Table 1.

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Funding: This study was supported by Bilateral BBSRC-Embrapa grant number BB/N01622X/1.

First and second authors contributed equally to this work.

*The e-Xtra logo stands for “electronic extra” and indicates that four supplementary tables and one supplementary appendix are published online.

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LEAF RUST RESISTANCE IN WHEAT

Many wheat loci conferring resistance to the three rust pathogens have been reported (see McIntosh et al. 1995, 2008). Those leaf rust resistance loci that have been determined as unique, being genetically distinct from pre-existing loci, are designated an *Lr* number. However, the majority of leaf rust resistance genes assigned an *Lr* gene number confer all-stage resistance (ASR) (Table 1). ASR is effective throughout the life of the plant. It is commonly qualitative (also referred to as major resistance) and associated with a programmed cell death defense

response referred to as hypersensitive immunity. However, ASR often proves to be race-specific; the resistance only being effective against *P. triticina* isolates carrying the corresponding avirulence gene, and short-lived; high levels of mutation and virulence diversity present within *P. triticina* populations resulting in these leaf rust resistance genes rapidly becoming ineffective (Lowe et al. 2011). Consequently, wheat cultivars with long-lasting leaf rust resistance has been hard to achieve using ASR genes alone. Many leaf rust ASR genes have proven ineffective within a few years of introduction, for example, the deployment of *Lr10* and *Lr16* in Canadian wheat cultivar Selkirk (*Lr10*, *Lr14a*, and *Lr16*).

FIGURE 1

Modified Cobb scale leaf rust infection scores on wheat cultivar Toropi. **A**, Resistant reaction (40R/3MR), **B**, moderate resistant reaction (40MR), **C**, moderate susceptible reaction (70MS), and **D**, susceptible reaction (100S).

TABLE 1
A glossary of the terms commonly used to describe the phenotypic differences between rust resistance loci

Adult plant resistance	Resistance that is not expressed at the two to three leaf seedling stage, but is expressed only at later stages in the plant's development
All stage resistance	Resistance that is expressed throughout the life of the plant
Partial resistance	Resistance that only confers a partial reduction in pathogen infection
Qualitative resistance	Resistance in which the expression is not influenced by genetic background or environmental variables
Quantitative resistance	Resistance in which the expression can be influenced by genetic background or environmental variables
Quantitative trait loci	The position in the plant genome where loci are found that confer a quantitative resistance
Race-non-specific resistance	Resistance that is effective against all known isolates of a pathogen
Race-specific resistance	Resistance that is effective against isolates of a pathogen carrying the corresponding avirulence gene
Slow rusting resistance	Resistance that slows the development of pathogen infection, extending the latent period and usually resulting in smaller pustules and fewer spores

Virulence to *Lr10* increased soon after the introduction of Selkirk, whereas virulence to *Lr16* started to increase 8 years after Selkirk was widely grown (McCallum et al. 2016). Combining ASR genes can prolong the effective life of rust resistant cultivars, but this runs the risk of creating races of rust isolates with multiple virulence, leading to hypervirulent pathogen populations.

Currently 15 leaf rust adult plant resistance (APR) genes have been given an *Lr* gene number designation. Seven *Lr* genes, *Lr12*, *Lr13*, *Lr22alb*, *Lr35*, *Lr37*, *Lr48*, and *Lr49* have proven to be race-specific, while the remaining eight are still considered race-non-specific (Table 2) (McIntosh et al. 1995, 2008). The race-specific APR genes *Lr12*, *Lr13*, and *Lr22b* are qualitative and associated with a hypersensitive cell death response but expressed only at later stages in the plant's development (McIntosh et al. 2008; Singh and Bowden 2011). A number of APR genes, while conferring only partial leaf rust resistance, have remained effective when deployed widely, for many years and in environments conducive to leaf rust. For example, the APR gene *Lr34* has proven to be durable, having been widely deployed in CIMMYT spring wheat cultivars (Singh et al. 2000). *Lr34* and *Lr46*, as well as APR *Lr67* are unique in that they confer partial resistance to all three rust species, as well as to powdery mildew, caused by *Blumeria graminis* f. sp. *tritici*. In addition, a number of these APR genes also exhibit a slow rusting phenotype, e.g., *Lr34*. The resistance retards the development of the pathogen (increased latent period) (Table 1), slowing the appearance of rust pustules, which generally tend to be smaller and produce fewer urediniospores (Singh et al. 2005).

The potential of APR to confer durable protection against the cereal rusts has gained great attraction since the pioneering work of R. M. Caldwell in the US and R. Johnson in the UK; work that today serves as a guiding principle in many research and breeding programs. The renewed interest in APR genes has accelerated the discovery of new quantitative trait loci (QTL) (Table 1), many conferring resistance toward all three rust pathogens of wheat (Lowe et al. 2011). However, a single QTL rarely confers adequate resistance, especially under high disease pressure, a combination of four or five QTL/genes being required to establish adequate levels of rust resistance (Singh et al. 2000). It is also important to understand how environmental variables impact each QTL's expression, and how the QTL interact, either positively or negatively, to influence the final rust resistant phenotype. Therefore, in quantifying the value of a QTL for rust resistance breeding it is important to consider the QTL's expression over a range of environments, across seasons and under different levels of disease pressure.

In this review we focus on quantitative leaf rust resistance in hexaploid wheat, as identified through field tests. The review covers

reports published between January 1971 and January 2018, and references 249 leaf rust resistance QTL. We review leaf rust resistance QTL identified in biparental and association mapping (AM) studies and compare with a QTL meta-analyses for leaf rust resistance published in 2015 (Soriano and Royo 2015). The aims of this review are therefore to summarize field, APR QTL for leaf rust.

QUANTITATIVE RACE-NON-SPECIFIC APR LOCI WITH *LR* DESIGNATIONS

Lr34/Yr18/Sr57/Pm38 (hereafter called *Lr34*) was first characterized in Canada by Dyck (1977, 1987), but *Lr34*-containing wheat germplasm has been used in the development of new wheat cultivars since the early part of the twentieth century. While the *Lr34* resistant phenotype can vary in different environments and genetic backgrounds, *Lr34* has remained durable for more than 50 years (Krattinger et al. 2009; Lagudah et al. 2009). *Lr34* was the first APR gene to be cloned (Krattinger et al. 2009). It encodes an ATP-binding cassette (ABC) transporter and currently two predominant alleles of *Lr34* have been found that differ by only two exon-polymorphisms (Krattinger et al. 2009; Lagudah et al. 2009). Three other haplotypes were described for *Lr34*, two being considered rare (Dakouri et al. 2010; Lagudah et al. 2009). Studies suggest that the resistant haplotypes are evolutionarily younger than the susceptible, and that it is unique to the wheat D-genome; *Lr34* being located on the short arm of chromosome 7D. Cloning of *Lr34* has enabled gene-specific DNA markers to be developed (Dakouri et al. 2010; Krattinger et al. 2009; Lagudah et al. 2009), providing a fast and powerful tool for marker assisted selection (MAS) in wheat breeding, allowing *Lr34* to be combined with other QTL and/or genes of interest.

Lr46/Yr29/Sr58/Pm39 (hereafter called *Lr46*) has been found extensively in wheat germplasm originating from CIMMYT (William et al. 2003). This gene is located on the long arm of chromosome 1B, being first identified in wheat cultivar Pavon 76 (Singh et al. 1998). *Lr46* was mapped distal to marker *Xwmc44* and proximal to *Xgwm259* in wheat cultivar Oligoculm (Suenaga et al. 2003) and between the SSR markers *Xwmc719* and *Xhbe248* in cultivar Saar (Lillemo et al. 2008). The *csLV46* marker (E. S. Lagudah, *personal communication/unpublished data*) is being used in MAS for the *Lr46* locus. While *Lr46* has a similar phenotype to *Lr34*, conferring multiple-pathogen resistance (Lillemo et al. 2008; William et al. 2003), the resistance conferred by *Lr46* is not as pronounced as *Lr34* in some environments (Kolmer et al. 2018a; Lagudah 2011).

The leaf rust APR gene *Lr67/Yr46/Sr55/Pm46* (hereafter called *Lr67*) was first identified in the Pakistan wheat accession PI250413

TABLE 2
List of adult plant resistance (APR) genes with designated leaf rust numbers identified in hexaploid wheat (*Triticum aestivum*) and currently considered race-non-specific

APR <i>Lr</i> gene	Chromosome	Cultivars	Reference
<i>Lr34</i>	7DS	Mentana/Ardito	Dyck 1977, 1987; Lagudah et al. 2009
<i>Lr46</i>	1BL	Pavon 76	Singh et al. 1998
<i>Lr67</i>	4DL	PI 250413	Dyck and Samborski 1979
<i>Lr68</i>	7BL	Parula/Frontana	Herrera-Foessel et al. 2012
<i>Lr74</i>	3BS	BT-Schomburgk	Chhetri 2016
<i>Lr75</i>	1BS	Forno	Singla et al. 2017
<i>Lr77</i>	3BL	Santa Fe	Kolmer et al. 2018b
<i>Lr78</i>	5DS	Toropi	Kolmer et al. 2018a

and transferred into Thatcher to produce the near-isogenic line RL6077 (Thatcher*6/PI250413) (Dyck and Samborski 1979). Hiebert et al. (2010) mapped *Lr67* in RL6077 to the long arm of chromosome 4D. *Lr67* can be found in Indian wheat cultivar Sujata (Lan et al. 2015) and NewPusa876 (Ponce-Molina et al. 2018b), and the CIMMYT cultivars Yaqui53, Chapingo48 and Chapingo53 (Moore et al. 2015). *Lr67* has been cloned, the protein resembling a predicted hexose transporter (LR67res). Although both the resistant, *Lr67res* and susceptible allele, *Lr67sus* are upregulated upon rust infection, only *Lr67res* confers resistance. LR67res differs from LR67sus by two amino acids in a region conserved across orthologous hexose transporters, which in turn reduces the proteins affinity for glucose. LR67res exerts a dominant-negative effect through heterodimerization, which is thought to reduce glucose uptake, thereby inhibiting colonization of plant tissues by biotrophic pathogens (Moore et al. 2015). Cloning of *Lr67* has enabled gene-specific DNA markers to be developed for MAS (Moore et al. 2015).

Other leaf rust APR genes that have been sufficiently characterized to be designated a *Lr* number include *Lr68*, *Lr74*, *Lr75*, *Lr77*, and *Lr78*. *Lr68* is an APR gene that was mapped on the long arm of chromosome 7B (Herrera-Foessel et al. 2012). Its origins can be traced back to Brazilian cultivar Frontana, which also possesses *Lr34* and *Lr13*. The markers *Psy1-1* (0.5 cM) and *Xgwm146* (0.6 cM) flank the *Lr68* locus but were not suitable for MAS (Herrera-Foessel et al. 2012). The codominant marker *cs7BLNLR* (0.8 cM) and the dominant marker *csGS* (1.2 cM) have subsequently been developed for *Lr68* (Herrera-Foessel et al. 2012).

Lr74 is an APR on chromosome arm 3BS, originally mapped in wheat selection BT-Schomburgk and cultivar Spark, it has also been found in wheat cultivar Caldwell (Kolmer et al. 2018c). The leaf rust APR *Lr75* is located on the short arm of chromosome 1B, first identified in Swiss cultivar Forno (Singla et al. 2017). Schnurbusch et al. (2004) reported six leaf rust resistance QTL in Forno, including *Lr34*. The locus *QLr.sfr-1BS* (*Lr75*) explained from 28 to 32% of the phenotypic variation when grown in Switzerland. A re-evaluation of the original mapping population from the cross Arina × Forno resulted in the designation of *QLr.sfr-1BS* as *Lr75* (Singla et al. 2017).

Lr77 was identified in hard red wheat winter cultivar Santa Fe on the long arm of chromosome 3B (Kolmer et al. 2018b). The locus is defined by the SNP marker *IWB10344* and confers r^2 values from 0.23 to 0.79. *Lr78* was identified in Brazilian cultivar Toropi on the short arm of chromosome 5D, designated by the SNP marker *IWA6289*. *Lr78* confers r^2 values up to 0.53 for leaf rust resistance (Kolmer et al. 2018a).

While these APR genes confer partial resistance, in combination with other APR genes, or ASR genes, greater resistance can be achieved. For example, the APR gene *Lr46*, in combination with the QTL *QLr.cdl-5BL* exhibited enhanced, additive resistance (Kolmer 2015). The ASR genes *Lr16* and *Lr23*, in combination with *Lr34*, have conferred effective leaf rust resistance for several years in hard red wheat cultivar Norm, even though alone these genes do not provide a significant level of resistance (Kolmer 2015; Tsilo et al. 2014). A complementary combination of ASR and APR genes is usually considered the most desirable for providing effective leaf rust resistance in the field, while potentially maintaining resistance durability (Lagudah 2011).

IDENTIFICATION OF LEAF RUST RESISTANCE QTL

A QTL is defined at a position in the genome where a gene/s is found that confers a quantitative phenotype, the expression of the gene being potentially influenced by other genes in the genetic background, e.g., epistatic interactions, and/or environmental factors (Table 1) (Lynch and Walsh 1998). QTL identification requires a plant population where the QTL are represented by

different alleles, each conferring a detectable, but different phenotype. The QTL is called when the mean resistance phenotype between plants carrying different alleles at that locus are significantly different. The population must also be sufficiently genetically diverse to enable polymorphic DNA markers associated with the QTL to be identified. Several populations types have been utilized for mapping of leaf rust resistance QTL, including F₂, backcrosses (BC), doubled haploid (DH), recombinant inbred line (RIL), near-isogenic line (NIL), multiparent advanced generation intercrosses (MAGIC), and association mapping (AM) populations. Each population type possesses advantages and disadvantages. In mapping populations derived from biparental crosses QTL detection is limited by the trait genetic diversity present within the two parents of the original cross (Xu et al. 2017). In addition, they usually represent limited recombination events, allowing the localization of QTL, at best to 10 to 20 cM intervals (Xu et al. 2017). Multiparent mapping populations have been constructed to overcome the limitations of biparental populations. The multiple genotypes (parents) used to develop the population allows the inclusion of multiple QTL, and QTL alleles, while repeated cycles of crossing increases the number of recombination events, allowing for greater mapping resolution.

To date most leaf rust resistance QTL have been identified using biparental mapping populations. More recently, AM panels have been used to widen the germplasm search for leaf rust resistance QTL. AM has enormous potential to process large collections of diverse germplasms, but usually requires follow-on confirmation, often through biparental mapping, to validate MTA (Prins et al. 2016). AM relies on the linkage between genes and molecular markers having been broken by many generations of recombination, with any remaining associations being due to close physical proximity. AM therefore overcomes two fundamental limitations of biparental mapping: the limited amount of recombination that occurs during the development of a biparental mapping population, which in turn influences the resolution of QTL positions, and the limited allelic diversity that segregates within a biparental cross. However, AM is prone to false positive QTL identification due to population structure and cannot detect rare alleles (<5%) within the AM panel (Korte and Farlow 2013).

The advances in DNA marker technologies mean that it is now possible to obtain good genetic maps for large genome species such as hexaploid wheat, with good marker coverage of most chromosomes, although the D-genome is still underrepresented due to low levels of DNA polymorphism (Gao et al. 2016; Li et al. 2015). With the 66 leaf rust resistance studies reviewed, we observed that SSR markers are still a popular choice in wheat due to their good coverage of the genome, codominant inheritance, high information content, simple detection and reproducibility (Supplementary Table S1). SSR markers are also a good marker to compare between genetic maps. However, SSRs are now being superseded in leaf rust resistance mapping studies by advanced, next-generation-sequencing (NGS) SNP marker technologies (Chhetri et al. 2016; Ponce-Molina et al. 2018a), including the use of the Illumina iSelect 9K and 90K SNP arrays (Zhang et al. 2017). These new marker technologies, along with the release of the hexaploid wheat RefSeq-v1.0 genome (<https://www.wheat-genome.org/>), provide accurate methodologies for locating QTL and comparing QTL locations across wheat genotypes.

Several statistical methods have been developed to detect QTL (Hackett 2002). A QTL is defined by its position on a genetic marker linkage map (centimorgans; cM), by its r^2 value (percentage of phenotypic variation explained – % PVE) and its LOD (logarithm of the odds) score. The value of r^2 shows the influence of the QTL on the phenotype, being the percent of the total phenotypic variance that is accounted for by the QTL associated markers. The LOD score is the statistical strength of

evidence for a QTL at a given location (Broman 2001). The term “major QTL” is often used to indicate that a QTL has a large effect on the phenotype and is usually detected in more than one environment. Some authors consider a QTL as “major” when it contributes at least 15 to 20% of the phenotypic variation segregating in the test population (Du et al. 2015). However, the same QTL can contribute differently to the phenotypic variance in different studies; i.e., different populations and growing environments.

SUMMARY OF REPORTED LEAF RUST APR QTL

In this review we report on 249 leaf rust resistance QTL as identified in 70 biparental mapping populations and 79 different donor lines, 35 meta-QTL (MQTL) (Supplementary Table S2) reported by Soriano and Royo (2015), and nearly 200 MTA/QTL (marker trait associations) identified in seven AM studies, covering all 21 chromosomes of hexaploid wheat (Table 3; Supplementary Table S3). The last review on this topic, Li et al. (2014), reviewed 27 studies in durum and bread wheat, reporting 80 leaf rust APR loci across 16 chromosomes (highlighted in bold in Supplementary Table S1).

An MQTL analysis was carried out by Soriano and Royo (2015) that incorporated 144 leaf rust resistance QTL identified in 20 biparental mapping populations. The mapping populations represented 33 parental lines, both bread and durum wheat cultivars, studied between 1999 and 2015 in 52 environments. This MQTL analysis integrated the results of these independent QTL studies, projecting the individual QTL onto a consensus map using QTL-associated markers common between the mapping populations

(Goffinet and Gerber 2000). Pooling the results of several studies through MQTL analysis increases statistical power and allows more precise estimation of genetic effects (Wu and Hu 2012). The MQTL analysis identified 48 regions, on 17 chromosomes, 35 of which represented two or more, closely linked leaf rust resistance QTL (128 QTL out of 144 QTL included in the meta-analysis), with the remaining 13 regions containing a unique QTL. Seven of the MQTL were found to colocalize with 11 designated *Lr* genes (*Lr10*, *Lr13*, *Lr14*, *Lr19*, *Lr23*, *Lr27*, *Lr34*, *Lr46*, *Lr67*, *Lr68*, and *Lr71*) (Soriano and Royo 2015).

Leaf rust resistance AM studies have been undertaken in 96 winter wheat genotypes (Gerard et al. 2018), 3,640 spring wheat genotypes (Elbasyoni et al. 2017; Gao et al. 2016; Kankwatsa et al. 2017; Turner et al. 2017), 295 mixed-type wheat genotypes (Riaz et al. 2018), and 173 synthetic hexaploid wheat genotypes (Jighly et al. 2016). These studies reported 175 MTA/QTL across 20 wheat chromosomes, with no associations reported on chromosome 3D (Table 3).

The B genome carries the greatest number of leaf rust resistance QTL (Fig. 2; Supplementary Table S4), with 133 QTL, mainly on chromosomes 1B and 2B (Fig. 2). Approximately 53% of the 249 QTL and 20 MQTL reported in biparental mapping studies are located on the B genome. The A genome has the lowest number of QTL for leaf rust resistance. Chromosomes 4A, 7A, 5D, and 6D have the fewest leaf rust resistance QTL (Fig. 2). The group 2 chromosomes carry 66 leaf rust resistance QTLs and 6 MQTL, with chromosome 2B also being well known for carrying disease resistance loci for stripe rust, stem rust, and powdery mildew (McIntosh et al. 1995, 2008).

TABLE 3
Summary of significant leaf rust resistance marker trait associations identified in hexaploid wheat by association mapping (AM)

Genomic source	Number of genotypes	Type of resistance assayed	Number of polymorphic markers	Number of MTA/QTL	Chromosome location	Genes predicted ^a	Genotyping technology	Reference
Spring wheat	2,111	Adult	3,215	36	1A, 2A, 2B, 2D, 3A, 5A, 5B, 6A, 7A	<i>trp-1</i> , <i>Lr11</i> , <i>Lr52</i> , <i>Lr47</i>	Illumina iSelect 9K SNP array	Elbasyoni et al. 2017
Elite spring wheat breeding lines	338	Seedling and adult	18,924	46	All (except 3D and 5A)	<i>Lr1</i> , <i>Lr3</i> , <i>Lr9</i> , <i>Lr11</i> , <i>Lr14</i> , <i>Lr17</i> , <i>Lr21</i> , <i>Lr26</i> , <i>Lr28</i> , <i>Lr30</i> , <i>Lr34</i> , <i>Lr38</i> , <i>Lr42</i> , <i>Lr64</i> , <i>Lr68</i> , <i>Lr72</i>	Illumina iSelect 90K SNP array	Gao et al. 2016
Winter wheat	96	Adult	874	13	1B, 1D, 2A, 2B, 2D, 3B, 4A, 5B/7B, 6A/6B, 7D	<i>Lr22</i> , <i>LrSV1</i> , <i>Lr27/Sr</i> , <i>LrSV2</i> , <i>Lr28/Sr7</i>	DARt	Gerard et al. 2018
Synthetic hexaploid wheat	173	Adult	6,176	5	1B, 1D, 2D, 6D, 7D	<i>Lr46</i> , <i>Lr42</i> , <i>Lr39</i> , <i>Lr38</i> , <i>Lr19</i>	DARt and DARt-Seq	Jighly et al. 2016
Spring wheat	159	Seedling and adult	5,688	23	1B, 1D, 3B, 4A, 5B, 6A, 6B, 6D, 7A	<i>Lr34</i> , <i>Lr46</i> , <i>Lr67</i> , <i>Lr68</i> , <i>Lr74</i>	Illumina iSelect 9K SNP array	Kankwatsa et al. 2017
Hexaploid wheat	295	Seedling and adult	10,748	31	1A, 1B, 2A, 2B, 3A, 3B, 4A, 5A, 5B, 6A, 6B, 7A, 7B, 7D	<i>Lr64</i> , <i>Lr3</i> , <i>Lr14b</i> , <i>Lr68</i> , <i>LrBi16</i> , <i>LrFun</i> , <i>Lr34</i>	DARt-Seq	Riaz et al. 2018
Spring wheat	1,032	Seedling and adult	5,732	37	All (except 1D, 3D, 6B, and 7B)	<i>Lr10</i> , <i>Lr11</i> , <i>Lr17</i> , <i>Lr27</i> , <i>Lr28</i> , <i>Lr30</i> , <i>Lr34</i> , <i>Lr35</i> , <i>Lr46</i> , <i>Lr63</i> , <i>Lr66</i> , <i>Lr67</i> , <i>Lr74</i>	Illumina iSelect 9K SNP array	Turner et al. 2017

^a Genes with no leaf rust resistance considered by the authors to be present in their AM germplasm.

The B genome is the largest of the wheat genomes and is highly diverged from the A and D genomes. The three ancestral genomes, although genetically related, i.e., homoeologous chromosomes capable of pairing at meiosis, have undergone considerable divergence and modifications since the first hexaploid was formed (Griffiths et al. 2006). The D genome shows the least differentiation relative to its progenitor *A. tauschii*, but in hexaploid wheat the D genome exhibits limited DNA polymorphism, presumably due to limited polyploidization events with tetraploid emmer wheat (*Triticum dicoccoides*; AABB) during its evolution (Nesbitt and Samuel 1996). However, the D genome donor is still available, *A. tauschii* having a geographic distribution that extends from northeastern Syria, Iran, Iraq, and Transcaucasia, to the western slopes of the Himalayas into China, and therefore represents a potential source of wide genetic diversity that could be introduced into hexaploid wheat (Haider 2013). The precise ancestor of the wheat B genome is unknown (Haider 2013). The A genome donor is believed to have been related to the diploid wild einkorn wheat *Triticum urartu*, although considerable gene loss has been reported on the A genome of hexaploid wheat compared with *T. urartu* (Ling 2013). This gene loss may explain why the A genome has so few leaf rust resistance loci compared with the B and D genomes in hexaploid wheat.

In the remainder of this review we describe the leaf rust resistance QTL identified in biparental mapping studies and the meta-analysis by chromosome group. The % PVE by each QTL is provided to give the reader an idea of the possible “strength” of the leaf rust resistance, although it must be remembered that other factor can influence the % PVE of a QTL, including the other leaf rust resistance genes segregating in the population in which the QTL was identified. Although QTL may appear to locate to what appears to be the same chromosome position, this could not be confirmed for most studies, as different marker systems have been used over the period being reviewed. Where QTL were reported as colocalizing with designated *Lr* genes we could ascertain that the

same leaf rust resistance QTL was being reported, e.g., for *Lr34* (7DS) (Fig. 2).

CHROMOSOME GROUP 1 LINKED QTL

Chromosomes 1A, 1B, and 1D homeologs possess 48 QTL and five MQTL, of which 11 QTL are located on chromosome 1A, 32 on chromosome 1B and 5 on chromosome 1D (Fig. 2). One MQTL was found on 1A and four on 1B (Fig. 2). The 11 QTL and one MQTL reported on chromosome 1A are derived from the wheat genotypes Apache, Opata 85, 842-2, Syn022L, Chapio, Shanghai 3/Catbird, Luke, and Sujata (Azzimonti et al. 2014; Du et al. 2015; Kumar et al. 2013; Lan et al. 2015; Leonova et al. 2008; Naz et al. 2008; Rosewarne et al. 2015; Zhou et al. 2014). *QLr.cau-1AS* explained from 44.3 to 52.6% PVE for leaf rust in wheat cultivar Luke when crossed with Aquileja, but only explained 22.3 to 32.8% PVE when crossed with AQ24788-83 (Du et al. 2015). RIL carrying *QLr.cau-1AS*, when grown in China (Beijing, Gansu and Shandong) exhibited a 55.5% reduction in final leaf rust severity compared with control lines. RIL possessing *QLr.cau-1AS* in combination with *Lr34* showed around a 78.5% reduction in final rust severity (Du et al. 2015). The MQTL1 on chromosome 1A colocalized with the ASR gene *Lr10* (Soriano and Royo 2015).

Lr46, on the long arm of chromosome 1B, is common in CIMMYT wheat germplasm (Lan et al. 2014; Rosewarne et al. 2012). *Lr46* confers broad-spectrum resistance to four biotrophic fungal pathogens: *P. tritici* (*Lr46*), *P. striiformis* (*Yr29*), *P. graminis* f. sp. *tritici* (*Sr58*) (Singh et al. 2013), and *Blumeria graminis* f. sp. *tritici* (*Pm39*) (Lillemo et al. 2008). The locus is also associated with premature senescence of leaf tips, commonly referred to as leaf tip necrosis (*Ltn2*) (Rosewarne et al. 2006). *Lr46* was reported in 20 studies from 19 wheat donor genotypes. In 13 studies *Lr46* was associated with the marker *csLV46*, which is used in MAS for *Lr46*. Based on the presence of the marker *csLV46* we considered a QTL to be a good candidate for *Lr46* (Fig. 2). However,

FIGURE 2

Total number of leaf rust resistance quantitative trait loci (QTL) found on each hexaploid wheat chromosome, as reported in 70 biparental mapping studies (dark blue columns) and one leaf rust QTL meta-analysis (MQTL; orange columns). Some QTL may be reported more than once, as different markers were used in each mapping study, making comparison of genome locations difficult. Where we were able to confidently identify QTL in independent studies as having the same chromosomal location, we report the unique QTL number on each chromosome (purple columns).

the effectiveness of *Lr46* depends greatly upon the genetic background and environment (Lan et al. 2015), being less effective at higher temperatures (Lagudah 2011; Rosewarne et al. 2015). *Lr46* explained from 2.9 to 74.5% of the total PVE in different mapping populations and under different experimental conditions. The MQTL5 on 1B colocalized with the APR gene *Lr46* (Soriano and Royo 2015). The APR *Lr75* (*QLr.sfr-1BS*) also mapped to chromosome 1B, but to the short arm, and is flanked by SSR loci *Xgwm604* and *Xswm27* (Singla et al. 2017). *Lr75* explained 28 to 32% PVE in the cross Arina × Forno when grown in Switzerland (Schnurbusch et al. 2004).

Five QTL have been reported on chromosome 1D in four studies, derived from the wheat genotypes Syn022L, Avocet-YrA, Quaiu 3, and Kenya Kongoni (Basnet et al. 2014; Calvo-Salazar et al. 2015; Naz et al. 2008; Ponce-Molina et al. 2018a). Two of these QTL were subsequently identified as the ASR genes *Lr21* and *Lr42* (Basnet et al. 2014; Naz et al. 2008). Working with a BC population derived from the synthetic wheat Syn022L, Naz et al. (2008) found a QTL on chromosome 1D that mapped close to the marker locus *Xbarc149*. This QTL conferred both seedling (*QLrs.B22-1D*) and field leaf rust resistance (*QLr.B22-1D*), reducing leaf rust symptoms by 46.3 and 43.6%, respectively (Naz et al. 2008). Although the seedling *QLrs.B22-1D* located to the same chromosomal region as *Lr21*, different seedling phenotypes were observed when inoculated with the same *P. tritricina* isolate. This would indicate either a new allele of *Lr21*, or a new ASR gene, independent, but located near *Lr21* (Naz et al. 2008).

CHROMOSOME GROUP 2 LINKED QTL

The group 2 chromosomes homeologs possess the greatest number of leaf rust resistance genes, 66 QTL and six MQTL, with 12 QTL on chromosome 2A, 31 on chromosome 2B, and 23 on chromosome 2D, and one MQTL was found on 2A, two on 2B and three on 2D (Fig. 2). To date, around 20 designated *Lr* genes have been mapped to group 2 chromosomes, many being ASR genes (McIntosh et al. 1995, 2008). The APR gene *Lr37* was translocated to the short arm of wheat chromosome 2A from *Triticum ventricosum* (Helguera et al. 2003). *QLr.inra-2Ab* was identified in cultivar Apache, explaining 5.6 to 12.2% of the PVE and colocalized with *Lr37* (Azzimonti et al. 2014). *QLr.hbau-2AS*, derived from cultivar Weimai 8 explained from 25.79 to 71.55% of PVE and mapped between the marker loci *Xcfd36* and *Xbarc1138*, within an interval of 2.58 cM (Wang et al. 2015).

There are seven designated *Lr* genes on chromosome 2B, three of which are the APR genes *Lr13*, *Lr35*, and *Lr48*, all of which are race-specific genes (McIntosh et al. 2008). *Lr35* is located near the centromere, while *Lr13* and *Lr48* are on the short arm of 2B (McIntosh et al. 1995). *Lr13* is no longer effective in Mexico and South America but continues to confer leaf rust resistance in Australia and Canada (Zhang et al. 2016). MQTL8 is a compilation of seven studies, all using wheat cultivars Apache and Creso, and is likely to be associated with *Lr13* (Soriano and Royo 2015). *Lr48* is a recessive race-specific APR gene that is associated with a hypersensitive response and has been mapped between SSR marker loci *Xgwm429b* and *Xbarc7* (Bansal et al. 2008). *Lr35* was transferred to hexaploid wheat from the diploid wild relative *A. speltoides*, and like *Lr48* confers a hypersensitive reaction upon infection with *P. tritricina* (Saini et al. 2002). A major QTL, *QLr.hebau-2BS* was also mapped on 2BS, but to a different location from *Lr13* and *Lr48* (Zhou et al. 2014). *QLr.hebau-2BS* was mapped in the cross Shanghai 3 × Catbird, being flanked by loci *XwPt8548* and *XwPt2314*, and conferred from 15.3 to 37.4% of the PVE. *QLr.inra-2B* explains from 15 to 35.6% of the PVE for leaf rust resistance in wheat cultivar Apache but is on the long arm of 2B (Azzimonti et al. 2014).

Chromosome 2D has eight designated *Lr* genes, with *Lr22a* derived from *A. tauschii* and *Lr22b* derived from *T. aestivum*

conferring race-specific APR (McIntosh et al. 1995, 2008). Of the 23 QTL identified on chromosome 2D the most effective were *QLr.lp.osu-2DS* (wheat breeding line CI 13227) and *QLr.inra-2D* (cultivar Balance), which explained 34.6 to 48.2% and 4.4 to 46.4% of the PVE, respectively (Azzimonti et al. 2014; Xu et al. 2005). *QLr.lp.osu-2DS* exhibits a slow rusting phenotype, having a prolonged latent period. RIL possessing *QLr.lp.osu-2DS* had a mean latent period of 13 days, while lines without the QTL had mean latent periods of 7.5 days.

CHROMOSOME GROUP 3 LINKED QTL

Seven designated *Lr* genes have been found on the group 3 chromosomes. Five are ASR genes; *Lr24*, *Lr27*, *Lr32*, *Lr63*, and *Lr66* and two APR genes; *Lr74* and *Lr77* (McIntosh et al. 1995, 2008). There are 30 QTL and five MQTL reported on group 3 chromosomes, six QTL on chromosome 3A, 17 on chromosome 3B, and seven on chromosome 3D. Three MQTL was reported on chromosome 3A and 2 on 3B (Fig. 2). *QLr.fcu-3AL*, derived from the synthetic hexaploid wheat line TA4152-60, explained between 10 to 18% of the PVE in field tests, but also exhibited leaf rust resistance in seedling tests, indicating a potential ASR gene (Chu et al. 2009).

On chromosome 3B, *QLr.sun-3BS* explained 2.4 to 36.7% of the total PVE in the BT-Schomburgk selection (Chhetri et al. 2016), while *QLr.ifa-3BS* explained 4.1 to 40.1% PVE (Buerstmayr et al. 2014) in wheat cultivar Capo. *QLr.ifa-3BS* also colocalized with the stripe rust QTL *QYr.ifa-3BS* for both RIL populations studied; Capo × Arina and Capo × Furor (Buerstmayr et al. 2014). *QLr.cin-3BS* was mapped in wheat cultivar Chapio and may be the same locus as *Sr2*, representing a multipathogen resistance gene (Rosewarne et al. 2015). Kolmer et al. (2018c) mapped an APR QTL on 3B in cultivar Caldwell, which is colocalized with the APR gene *Lr74*. Li et al. (2017) also reported a QTL (*QLr.hwwg-3B.1*) on 3B that explained 16.6 to 19.2% of PVE and was provisionally identified as *Lr74*.

QLr.cin-3DC is the most effective leaf rust APR locus found on chromosome 3D. It explained from 17.8 to 25.4% of the PVE in wheat cultivar Francolin#1 (Lan et al. 2014). *QLr.tam-3D* only explained 4.0 to 7.1% of the leaf rust PVE in the wheat line Quaiu 3 but did colocalize with the yellow rust QTL *QYr.tam-3D* (Basnet et al. 2014).

CHROMOSOME GROUP 4 LINKED QTL

Twenty-five QTL and five MQTL have been reported on the group 4 chromosomes (Fig. 2). Two QTL were found on chromosome 4A, 14 on chromosome 4B and nine on chromosome 4D. For MQTL, one was reported on chromosome 4A, two on 4B and two on 4D. There are two designated *Lr* genes reported on 4A, the ASR genes *Lr28*, derived from *A. speltoides* and *Lr30* from *T. aestivum* (McIntosh et al. 2008). Zhang et al. (2017) reported a minor QTL in Chinese Spring (*QLr.hebau-4AL*) that explained 3.4 to 7.5% of the PVE.

Chromosome 4B carries the race-specific APR gene *Lr12*. *Lr12* cosegregates with the ASR gene *Lr31*. However, *Lr31* only confers leaf rust resistance when the complementary gene, *Lr27* (3BS) is present (Singh et al. 1999). Previously some confusion prevailed over the arm location of *Lr12* and *Lr31* on chromosome 4B (Singh et al. 1999; McIntosh et al. 2008), however, subsequent studies (Singh and Bowden 2011) mapped *Lr12* to the long arm of chromosome 4B, flanked by the marker loci *Xgwm251* and *Xgwm149*.

There are 14 QTL for leaf rust resistance on chromosome 4B, with PVE ranging from 5.4% (*QLr.spa-4B*) to 24.4% (*QLr.hebau-4B*). *QLr.spa-4B* was flanked by markers *wPt-5303* and *wPt-1849* and is derived from cultivar Carberry. *QLr.hebau-4B* was reported

in cultivar Chinese Spring linked to the markers BS00022181_51 and Excalibur_c37565_709, mapping to the same region of chromosome 4B as the race-specific APR *Lr12*. *QLr.cim-4BS* was found in cultivar Chapio and is also thought to map in the region of *Lr12* (Rosewarne et al. 2015; Singh and Bowden 2011). The APR *Lr49* maps to 4B and is associated with a hypersensitive response (Bansal et al. 2008; Saini et al. 2002).

Chromosome 4D possesses *Lr67*, an APR gene which was originally transferred from PI250143, a Pakistani wheat accession, into the Thatcher NIL RL6077 (Dyck and Samborski 1979). *Lr67* is associated with the leaf-tip necrosis, *Ltn3* (Herrera-Foessel et al. 2014), and colocalizes with MQTL20, which is a compilation of three QTLs from PI250143, cultivar Sujata and the synthetic line TA4252-60 (Soriano and Royo 2015). In field trials *Lr67* explained between 33.6 and 57.9%, and 20 to 44.5% of the total PVE in cultivar Sujata and wheat line W195, respectively (Chhetri et al. 2016; Lan et al. 2015). Four other, minor effect QTL were identified on chromosome 4D: *QLr.inra-4Da*, *QLr.B22-4D*, *QLr.fcu-4-DL*, and QTL-4DL.

CHROMOSOME GROUP 5 LINKED QTL

Twenty QTL and two MQTL were found on the group 5 chromosomes, five QTL on 5A, 13 on 5B and three on 5D, with the two MQTL being located on 5B (Fig. 2). There are currently no designated *Lr* genes cataloged on 5A (McIntosh et al. 2008), although minor leaf rust resistance QTL have been reported. Two QTL derived from cultivar Avocet have been identified in separate studies; *QLr.cim-5AC* (5% PVE; Calvo-Salazar et al. 2015) and *QLr.cimmyt-5AL* (5.2 to 7.4% PVE; Rosewarne et al. 2012). Both QTL mapped close to the centromere on 5A. *QLr.pbi-5AS* in cultivar Beaver, *QLr.sfrs-5AS* in cultivar Forno, and *QLr.hwwg-5AS* in cultivar Ning7840 are all located on the short arm, explaining 11.2, 7.7, and 7.5% of the PVE, respectively (Li et al. 2017; Messmer et al. 2000; Singh et al. 2009).

Kumar et al. (2013) found two minor APR QTL on 5B in Opata85, *QLr.ccsu-5B.4* (2.5 to 8.4% PVE) and *QLr.ccsu-5B.5* (4.4 to 7.3% PVE) that were consistently observed over multiple environments and years in India. Two consistently expressed APR QTL were also found in cultivar Jamestown that explained 1.7 to 22.1% (*QLr.vt-5B.1*) and 3.3 to 5.5% (*QLr.vt-5B.2*) of the total PVE. MQTL22 and MQTL23 on 5B are comprised of the QTL mapped in Kariaga and SHA3/CBRD; and Americano 25e, Capo, Carberry, and TA4152-60, respectively (Soriano and Royo 2015).

Ponce-Molina et al. (2018a) reported a significant QTL for leaf rust resistance on chromosome 5DS (*QLr.cim-5DS*) in wheat cultivar Chilero that accounted 5.2 to 34% of PVE. *QLr.cim-5DS* also collocated with a stripe rust resistance QTL (*QYr.cim-5DS*). In the old Brazilian wheat cultivar Toropi, a major APR QTL, subsequently designated *Lr78*, was mapped on 5DS. *Lr78* explained between 37 to 53% of PVE for leaf rust resistance in Toropi (Kolmer et al. 2018a).

CHROMOSOME GROUP 6 LINKED QTL

The group 6 chromosomes have the smallest number of reported leaf rust resistance QTL, with 16 QTL and five MQTL. Six QTL are found on chromosome 6A, seven on 6B and three on 6D. One MQTL was reported on chromosome 6A and four on 6B (Fig. 2). Two QTLs were identified in cultivar Avocet in two separate studies; *QLr.cimmyt-6AL* (William et al. 2006) explained from 4.2 to 6.3% and *QLr.cim-6AL* (Ren et al. 2017) from 8.5 to 12.6% of the total PVE. *QLr.cim-6AL* is collocated with the stripe rust resistance QTL, *QYr.cim-6AL*. Li et al. (2017) reported a minor QTL on 6AS (*QLr.hwwg-6AS*) in cultivar Clark, that explained between 5.0 to 7.1% of PVE.

Of the seven QTL on chromosome 6B, *QLr.inra-6B*, derived from cultivar Balance, explained from 3.4 to 29.2% of leaf rust resistance PVE, and cosegregated with the yellow rust resistance QTL *QYr.sun-6B* (Azzimonti et al. 2014).

The synthetic wheat Syn022L and the wheat line HD29 are the only hexaploid wheat genotypes where quantitative leaf rust resistance has been found on chromosome 6D. *QLrs.B22-6D* from Syn022L is an ASR, although only explaining 3.2% of the PVE in seedling tests, while in field trials *QLr.B22-6D* confers 2% of the PVE (Naz et al. 2008).

CHROMOSOME GROUP 7 LINKED QTL

Forty-three QTL and seven MQTL have been reported on chromosomes 7 homeologs, three on 7A, 19 on 7B and 21 on 7D (Fig. 2). For MQTL, one was identified on chromosome 7A, four on 7B and two on 7D (Fig. 2). However, of the 21 QTL reported on chromosome 7D, 19 correspond to *Lr34*. On 7A, Azzimonti et al. (2014) identified the QTL *QLr.inra-7Aa* in cultivar Balance that conferred 10.0 to 69.4% of the PVE; however, this was later found to be an ASR gene and designed *Lr20*. A minor QTL on 7A, derived from the breeding line MN98550-5 and conferring 2.2 to 8.1% of PVE was reported by Tsilo et al. (2014).

Four of the reported 19 QTL on chromosome 7B are probably *Lr68*. *Lr68* is a slow rusting resistance gene and is associated with a leaf tip necrosis phenotype (Herrera-Foessel et al. 2012). *QLr.hbu-7BL* (cultivar Fuyu 3) and *QLr.hwwg-7BL* (wheat line CI13227) collocate with *Lr68* and explained between 4.1 to 4.3% and 6.3 to 13.9% of PVE, respectively. *QLr.sfr-7B.1* (cultivar Forno) and *QLr.ksu-7BL* (cultivar Opata 85) are large effect APR QTL, each explaining 35.8% and from 11.0 to 42.2% of PVE, respectively (Faris et al. 1999; Messmer et al. 2000). The MQTL33 on chromosome 7B consisted of 11 QTL that originate from wheat cultivars Colosseo, Creso, and Sujata (Soriano and Royo 2015). MQTL33 colocalizes with the ASR genes *Lr14*, *Lr19* and the APR *Lr68*.

Lr34 on 7DS was reported in 19 publications, explaining from 8.0 to 75.2% of the PVE, depending on the cross and environment. *Lr34* was first described in Brazilian cultivar Frontana and could be traced to Italian cultivar Mentana (Lagudah et al. 2009). In the meta-analysis of Soriano and Royo (2015) *Lr34* corresponded to the MQTL34. Two minor APR QTL have also been mapped on 7D, *QLr.cim-7DS* in cultivar Francolin#1 and *QLr.hebau-7DS* in cultivar Naxos.

CONCLUSION

Leaf rust is a major, global threat to wheat production. To date the control of leaf rust has primarily been through the use of fungicides and the deployment of major, ASR genes. However, increasing reliance on ASR is proving inadequate to achieve effective resistance throughout the commercial life of a wheat cultivar, while resulting in pathogen populations with ever increasing complex virulence profiles. With more ASR genes rapidly becoming ineffective and fewer ASR genes being found to replace them, wheat breeders are turning their attentions to quantitative sources of leaf rust resistance.

The work of CIMMYT (Singh et al. 2000) has clearly shown that effective leaf rust resistance can be achieved by combining four to five quantitative resistance QTL together. In selecting suitable resistance QTL to combine together one must know whether starting materials contain the same or different sources of resistance, how stable the expression of each resistance source is in different environments, and whether there is a positive or negative interaction between different resistance genes/QTL.

Numerous studies of field, quantitative leaf rust resistance have been published in a very wide range of wheat germplasm.

However, these reports are rarely systematically analyzed, summarizing the genetic diversity underlying quantitative resistance in hexaploid wheat to the leaf rust pathogen *P. tritricina*. In this review we summarize all published sources of quantitative leaf rust resistance, found in hexaploid wheat, that have shown to be effective under field conditions. The potential value of each leaf rust resistance QTL reported is assessed in terms of the percentage phenotypic variance explained by the QTL in the specific wheat cross, and across multiple environments and years, where tested. This review therefore provides wheat pathologists and breeders with a summary of the potential sources of quantitative leaf rust resistance available in a wide range of wheat genotypes, enabling them to select those QTL most appropriate to their requirements.

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